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The Life Cycle of Evidence for Novel Chemotherapeutic Agents in Advanced Non-small Cell Lung Cancer

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The Life Cycle of Evidence for Novel Chemotherapeutic Agents in Advanced Non-Small Cell Lung Cancer

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Abstract

Problem: The failure of evidence to be translated in practice is sometimes referred to as the research-practice gap and can result in the inefficient use of limited health care resources.

Methodology: The thesis investigated the role of evidence in determining clinical recommendations and practice in lung cancer care. This was accomplished by simultaneously comparing the results of a systematic review of evidence, cumulative meta-analysis, recommendations, key milestones, and physician prescription database.

Results: There was limited evidence found in the literature for two novel chemotherapeutic agents (NCA) in combination with platinum chemotherapy for the treatment of advanced non-small cell lung cancer (NSCLC). Despite this, clinical recommendations for the use of these NCA were made within relatively short periods of time. There was rapid adoption of both NCA relative to recommendations by Ontario oncologists.

Conclusion: Evidence-practice gaps in the treatment of advanced NSCLC are short and may even be premature or inappropriate.

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I would like to thank the members of the Department of Epidemiology and the Ulysses program for your guidance and collegiality over the past few years that have led to my completion of the program and this thesis.

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Glossary

AACR: American Association for Cancer Research

ASCO: American Society of Clinical Oncology

BSC: best supportive care

CCO: Cancer Care Ontario

CIHR: Canadian Institute for Health Research

CISTI: Canada Institute for Scientific and Technical Information

Clinical recommendations-practice gap: the transfer of clinical recommendations into practice (see research-practice gap)

CMA: cumulative meta-analysis

CPG: clinical practice guidelines

Cross-over trials: a method of comparing two or more treatments or interventions in which the subjects, upon completion of the course of one treatment, are switched to another.

Cumulative meta-analysis: methodology where a new meta-analysis is performed every time a new trial is added to a series of trials to evaluate the impact of each trial

DSG: Disease Site Groups

ECOG: Eastern Cooperative Oncology Group

EORTC: European Organization for Research and Treatment of Cancer

ECCO: European Cancer Conference

Error, Type I: (syn: alpha error) the error of rejecting the null hypothesis, i.e., declaring that a difference exists when it does not

ESMO: European Society of Medical Oncology

FDA: Food and Drug Administration (U.S.)

GG: Guideline Groups

HR: Hazard Ratio: a form of relative risk; in survival analysis it is a summary of the difference between two survival curves, representing the reduction in the risk of death on treatment compared to control, over the period of follow-up.

KT: knowledge translation

LCECC: Life Cycles of Evidence in Cancer Care

NCA: novel chemotherapeutic agents

NCI: National Cancer Institute US

NCIC: National Cancer Institute of Canada

NDFP: New Drug Funding Program

NSCLC: Non-small Cell Lung Cancer

NOC: Notice of Compliance

OHRI: Ottawa Health Research Institute

OPIS: Oncology Patient Information System

PDQ: Physician Data Query: an online system that outlines recommended treatments for cancer

PEBC: Program in Evidence- Based Care

Phase II trial: pilot study to evaluate safety and efficacy, can be randomised but not always

Phase III trial: extensive trial for complete assessment of safety and efficacy usually randomised and multicenter

RCT: Randomised controlled trials: An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not to receive an experimental prevention or therapeutic procedure, manoeuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. Randomised control trials are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology.

Research-clinical recommendations gap: the transfer of research into clinical recommendations (see research-practice gap)

Research–practice gap: The failure of the results of clinical trials to be incorporated into practice or the premature adoption of unproven treatments

SCLC: small cell lung cancer

SWOG: Southwest Oncology Group

TNM classification: staging system that uses a combination of tumour size/location (T), degree of nodal spread (N) and evidence of metastatic disease (M)

WCLC: World Conference on Lung Cancer

Preamble

This thesis represents a pilot study for the Canadian Institutes for Health Research (CIHR) funded project entitled, "The Life Cycle of Evidence in Cancer Care" (Principal Investigators Dr. J. Grimshaw and Dr. I. Graham). The objective of the CIHR project is to investigate the relative role of evidence in determining clinical recommendations and practice in cancer control, in particular breast cancer and lung cancer. The objective of the pilot study was to document the research-practice gap in cancer care and demonstrate the feasibility of the project through two case studies of the use of novel chemotherapeutic agents in non-small cell lung cancer.

As a member of the Life Cycles project research team, I actively participated in all phases of the project. I contributed to the development of the research grant submission and project protocol development. For the thesis, I helped develop and test the electronic search strategies (with assistance of Jessie McGowan, Information Scientist, Institute of Population Health, University of Ottawa), screened the results of electronic searches (with Munira Nurbhai, Research Co-ordinator and Sabbah Master, Summer Student, Clinical Epidemiology Program, Ottawa Health Research Institute), abstracted data from all included studies (Munira Nurbhai or Sabbah Master undertook dual independent data abstraction), undertook the cumulative meta-analysis (supervised by Keith O'Rourke, Scientist, CEP, OHRI), identified key milestones, guideline and textbook recommendations (with Munira Nurbhai and Jennifer Pierce, Summer

Student, CEP OHRI), and negotiated access to CCO OPIS database (with assistance of Mark Gregus from Cancer Care Ontario). Throughout my thesis project, I was supervised by Drs Jeremy Grimshaw and Ian Graham, (CEP OHRI) and supported as needed by other members of the Life Cycles project team (Dr. Bill Evans, Dr. Eva Grunfeld, Lorenzo Moja, Doug Coyle). I am responsible for all of the analyses presented in this thesis.

The thesis contains four chapters structured around the results of the pilot study. The study results are presented as two articles in Chapters 2 & 3 respectively. Chapter 1 provides a review of the literature of knowledge translation and discusses the context of the pilot study. Chapter 2 is formatted as a pre-publication article. It addresses the research-clinical recommendations gap through two case studies by reporting the results of a systematic review, cumulative meta-analysis and review of recommendations and key milestones. Chapter 3, a second pre-publication article, addresses the clinical recommendations-practice gap through comparison of data obtained in chapter 2 to the physician prescription data from the Ontario Oncology Patient Information System database. The final chapter summarizes the key findings of the pilot study, discusses the feasibility issues and makes preliminary suggestions based on these findings.

1. Chapter 1 - Introduction

1.1. Rationale

1.1.1. Knowledge transfer

The findings of health research will not change individual and population outcomes unless health services and health care professionals adopt them in practice (1). Despite the considerable resources devoted to health science, a consistent finding from the literature is that the transfer of research findings into practice is often a slow and haphazard process (2).

Patients may be denied treatments of proven benefit when the transfer of research into practice is inappropriately long. Alternatively, patients may be exposed to potentially ineffective and even harmful treatments when premature transfer of research occurs before the treatment is proven to be effective, or when delay occurs in withdrawing treatments proven to be ineffective or harmful. These scenarios result in the inefficient use of limited health care resources.

Increasing recognition of the research–practice gap has led to increased policy and research interest in knowledge transfer. For example, in 2000, the Parliament of Canada passed the Canadian Institute for Health Research Act (Bill C-13) (3) creating the Canadian Institute for Health Research (CIHR) giving it the mandate to "*excel, according to internationally accepted*

standards of scientific excellence, in the creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened Canadian health care system". The CIHR is composed of 13 "virtual" institutes (networks of researchers brought together to focus on important health problems) of which Cancer Research is one. As well, in keeping with its mandate, CIHR has developed a separate Knowledge Translation Branch that works closely with all the institutes.

The CIHR Act defines knowledge translation (KT) as a broad concept encompassing all steps between the creation of new knowledge and its application to yield beneficial outcomes for society (3). This definition includes knowledge management, utilization, and development of guidelines and dissemination. The scientific director of each of the 13 CIHR institutes is responsible for creatively integrating KT into relevant activities. The KT branch provides inspiration, knowledge and coordination to the institutes. In particular, the KT branch is to assist with funding and training of KT researchers and also to help develop KT networks within the CIHR and outside the CIHR including the public sector. This thesis is a pilot of a project entitled "The Life Cycles in Cancer Care" (henceforth to be called The Life Cycles project) (Principal Investigators Drs. Jeremy Grimshaw and Ian Graham) supported by a CIHR grant; its goal is to investigate knowledge translation in cancer care over time.

1.1.2. Evidence gaps

The failure of clinical trials results to be incorporated into practice or the premature adoption of unproven treatments is sometimes referred to as the **research-practice gap** (4). To better understand how this phenomenon might occur, the research-practice gap can be subdivided into the **research-clinical recommendations gap** (the transfer of research into clinical recommendations) and the **clinical recommendations-practice gap** (the transfer of clinical recommendations into practice).

Research-clinical recommendations gap

Antman & Lau examined the temporal relationship between accumulated results from randomised controlled trials of myocardial infarction treatments and the recommendations of clinical experts writing review articles and textbooks (5). They used the methodology of cumulative meta-analysis (CMA), where an updated meta-analysis is performed every time a new trial is added to a series of trials (6). When studies are accumulated by their publication year, the impact of each study added can be assessed and the earliest year at which the treatment effect becomes statistically significant established. They also plotted in parallel, by publication year, the recommendation of experts in review publications. Their study found considerable delays between the generation of evidence and when clinical experts made treatment recommendations in line with the new research findings.

For example, by 1973 the CMA included 10 trials that randomised 2544 patients (Figure 1-1) and demonstrated that thrombolytic drugs reduced mortality. However, it took 1986, for more than half the review articles and textbooks to recommend thrombolytic drugs, 13 years after they were shown to be effective by CMA. By that time, a total of 43 trials had been reported (10 in 1986 alone) with a total of 21 059 patients. Furthermore, in 1982 a meta-analysis showing an impressive reduction in mortality by thrombolytic therapy had been published in the New England Journal of Medicine (7). In fact, two large very large trials with a "no treatment" control group (GISSI-1 and ISIS-2) were started after 1982 (8, 9).

Antman and Lau's work also revealed an example of a case where a potentially harmful therapy continued to be recommended. For over 25 years, the majority of authors recommended lidocaine for prophylaxis against ventricular fibrillation, yet there was a non-significant increase in mortality associated with the use of lidocaine in the nine controlled trials conducted between 1970 and 1990 (Figure 1-2).

Clinical recommendations-practice gap

Antman & Lau demonstrated that with a common disorder such as cardiovascular disease, inefficiencies in knowledge synthesis and translation resulted in delays between the production of knowledge and its incorporation

into recommendations. This led to patients being denied effective interventions and offered potentially harmful interventions. Furthermore, scarce research resources were used inefficiently to continue to address questions where the answer was already known (5, 10). However, their study did not examine the clinical recommendations-practice gap. Was the thrombolytic therapy being adopted prior to or after the recommendations and what was the length in time of this gap? Conversely, was the use of lidocaine being abandoned prior to or after recommendations were changed?

Others have highlighted the existence of the clinical recommendations-practice gap. Grol et al. reviewed the development and implementation of national guidelines in the Netherlands. They explored the knowledge and acceptance of guidelines by performing 'before and after' surveys of family physicians (11). In general, they found that there was high knowledge and acceptance (~67%) but that there was significant variability in implementation. For instance, while rates of cervical screening improved with the introduction of guidelines, screening rates only went from 7% to 30%. This was confirmed by McGlynn et al. who performed a large survey and chart review of over 6000 adult Americans in 12 metropolitan centers to determine the quality of care using 439 indicators in 30 acute and chronic diseases (12). Only 54.9% receive the recommended care for these diseases. Both of these studies have shown that there is a gap between what is being recommended as standard of care and the actual practice of physicians.

1.1.3. Diffusion of Innovations

Novel medical therapies, such as thrombolytics, represent new technologies or innovations. Innovations also refer to, for example, preventative measures, diagnostic tools or interventions to disseminate information. An innovation does not need to be "new" with respect to time from conception, but merely the perception of being "new" by the potential adopter (13). The process by which the innovation spreads in a population of potential adopters is termed "diffusion" (14)

Ryan and Gross first gave substance to a 'diffusion of innovation theory' in 1943 with a study in agriculture (15). The authors documented the adoption of hybrid corn seed in Iowa over time and charted an adoption curve. The adoption curve and rates of adoption have subsequently been repeated in many different fields ranging from sociology to business to medicine.

Rogers (13)defined the key elements of diffusion theory to be: the process by which (1) an *innovation,* (2) is *communicated* through certain *channels*, (3) over *time, and* (4) among members of a *social system.* Diffusion can result in either adoption or rejection of the innovation.

Adoption is determined through the *innovation-decision process* which Rogers conceptualized in five main steps: (1) *knowledge* of the innovation's

existence, (2) *persuasion* when the potential adopter develops a favourable or unfavourable attitude towards the innovation, (3) *decision* when the potential adopter engages in activities that leads to either adoption or rejection, (4) *implementation* when the adopter puts the innovation to use, and (5) *confirmation* where the adopter seeks reinforcement of an innovation-decision and may still reject the innovation.

There are differing rates of adoption by those who adopt innovations. When cumulative number of adopters is plotted over time most innovations assume an S-shaped rate of adoption (Figure 1-3). Thus adopters can be categorized using a classification such as: (1) innovators, (2) early adopters, (3) early majority, (4) late majority, and (5) laggards.

With respect to the research-practice gap, this thesis will focus on the diffusion of innovations in cancer care. It will determine the timing and rates of adoption for different drugs in a population. It will also allow us to attempt to determine the magnitude and direction of the existing gaps, the pattern of adoption, and classification of subpopulations of adopters. This study is the first study to combine both: the generation of evidence and its translation into recommendations; as well as the subsequent adoption and diffusion of a therapeutic innovation in oncology.

1.2. Study Context

Cancer is a common disease that affects one third of the adult population with a mortality rate of approximately 50% for those affected. Ford et al. suggest that cancer, more than any other disease, defines state-of-the-art therapy through clinical trial results (14). This leadership in clinical trials likely has resulted from coordinated national and international clinical trial cooperative groups such as: National Cancer Institute of Canada (NCIC); National Cancer Institute US (NCI); Eastern Cooperative Oncology Group (ECOG); Southwest Oncology Group (SWOG); and the European Organization for Research and Treatment of Cancer (EORTC). How efficiently is the knowledge gained through these clinical trials transferred into practice?

The question about the application of research into practice within cancer care has been identified as an important issue (16). Ford et al. estimated that cancer outcomes could be improved by 30% with optimum application of what we currently know and that at least a 10% reduction in cancer mortality could be achieved through widespread use of available "state-of-the-art therapies" (14).

The 1988 reauthorization of the National Cancer Act in the USA highlighted the existence and importance of the clinical recommendations-practice gap in cancer. The Act requires the National Cancer Institute to report to Congress

about the extent to which new advances in cancer therapy are being incorporated into practice. Furthermore, to promote the rapid transfer of clinical recommendations into practice in the USA, initiatives such as the NCI's Physician Data Query (PDQ) (an online system that outlines recommended treatments for cancer) were established in the mid and late 1980s.

In Canada, Cancer Care Ontario has implemented a Program in Evidence-Based Care (PEBC) to bridge the research-practice gap. The PEBC's role includes: developing evidence-based care information for health care providers and the public; maintaining the quality and currency of evidence resources; ensuring the availability and accessibility of evidence resources; and disseminating and evaluating evidence resources (www.cancercare.on.ca). The program is coordinated through Disease Site Groups (DSG) and Guideline Groups (GG). These groups develop practice guidelines and evidence summaries for publication in peer review journals and also on the Internet.

Ford et al suggest that these strategies have had limited (although at times important) success in promoting the diffusion and adoption of cancer therapies suggesting the resiliency of this gap to amelioration (14). Raby et al. surveyed Canadian physicians about their beliefs on the role of

chemotherapy in the management of advanced Non-small Cell Lung Cancer (NSCLC). Their results demonstrated that only 40% of physicians believed chemotherapy improved survival and less than 20% of physicians recommended chemotherapy. This suggested that physicians were either unaware of the results of relevant clinical trials, or did not agree with them (17).

MacKillop et al. obtained similar results from a population-based study of the use of radiotherapy in NSCLC in Ontario over a 10 year period. This study revealed an overall trend toward lesser use of radiotherapy and chemotherapy for this condition, a trend that was contrary to the findings of most of the clinical trials and recommendations published in the North American medical literature during the same period (18).

Graham et al. surveyed Canadian oncologists about their attitudes and self-reported use of clinical guidelines (19). Similar to the results of Grol et al. (11), they found that there was high acceptance of the guidelines (~80%) but much lower self-reported use of the guideline recommendations (41%). Factors correlated to guideline use included training characteristics of physicians and attitudes towards guidelines. Therefore, there appears to exist

a clinical recommendations-practice gap within the Canadian cancer care system.

Lung Cancer

Lung cancer remains the most common cancer diagnosis and cause of cancer related death in North America (20, 21). Non-small cell lung cancer (NSCLC) represents 75-80% of these cases and the majority of patients present with advanced disease. Physicians determine advanced disease in NSCLC by using the TNM staging system that uses a combination of tumour size/location (T), degree of nodal spread (N) and evidence of metastatic disease (M) to come up with a TNM classification (see Appendix A) (22). TNM classifications are grouped into stages between I and IV. Stage IIIB and IV are referred to as advanced disease.

Either curative surgery or curative radiation alone is not a choice for advanced stage disease. The prognosis is extremely poor with approximately only 10% of untreated patients living to a year. Palliative chemotherapy has been shown to provide patients with advanced NSCLC with both a survival and quality of life advantage (23). Until the 1990s, the mainstay of treatment for advanced NSCLC was symptom control either with palliative radiotherapy or systemic chemotherapy. Older chemotherapeutic agents (such as alkylating agents) had not shown any consistent survival advantage. However, the advent of platinum chemotherapeutic agents provided

encouraging results. A meta-analysis of palliative chemotherapeutic agents in treating NSCLC demonstrated that including a platinum agent is the key to providing a modest survival advantage (24). However despite identifying the optimal chemotherapeutic agent, both response rates (<30%) and survival advantages (6 weeks) remained modest.

In an ongoing effort to improve on these results, the 1990's saw the emergence of novel chemotherapeutic agents (NCA) such as vinorelbine, gemcitabine, paclitaxel and docetaxel which have been used as single agents or in combination with platinum chemotherapeutic agents (cisplatin or carboplatin) in treating advanced NSCLC. Platinum in combination with a NCA have shown statistically significant improved survival over combinations of a platinum agent and older chemotherapies in NSCLC (25-27).

1.3. Goals

In a series of 2 articles, this thesis will present the results of a pilot study of the CIHR funded grant The Life Cycle of Evidence in Cancer Care (henceforth referred to as The Life Cycle project) lead by principal investigators Dr. Jeremy Grimshaw & Dr. Ian Graham. The objective is to investigate the relative role of evidence in determining clinical recommendations and practice in cancer control. The pilot study focused on the treatment of advanced NSCLC with two novel chemotherapy agents

(NCA) in combination with a platinum chemotherapy agent. The study documented the evolution of evidence and compared this to the corresponding recommendations and key milestones over time. The study simultaneously compared the evidence, recommendations, milestones and diffusion of these NCA into the practice of the Ontario regional cancer care system. This study will provide the first study in cancer care to provide the life cycle of evidence across the whole continuum of the research-practice gap.

1.4. Objectives

In order to accomplish this task, the thesis will:

- perform a systematic review of the evidence demonstrating efficacy of two NCA in combination with a platinum agent for first line therapy in advanced NSCLC;
- conduct a CMA of the efficacy of each NCA;
- identify recommendations and key milestones in the life cycle of the evidence of each NCA and determine if there is a research-clinical recommendations gap;
- determine the time it takes for the evidence to be incorporated (or not) into clinical practice and determine if there is a clinical recommendations-practice and/or research-practice gap.

Figures

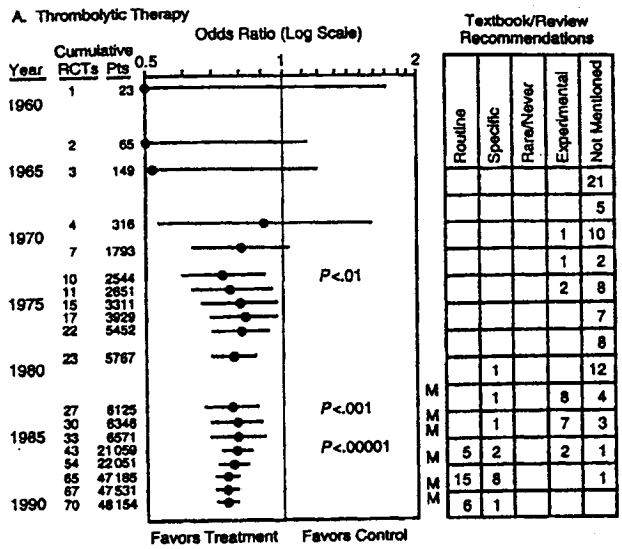


Figure 1-1 Cumulative meta-analysis thrombolytics for myocardial infarction

(Antman et al. 1992 (10))

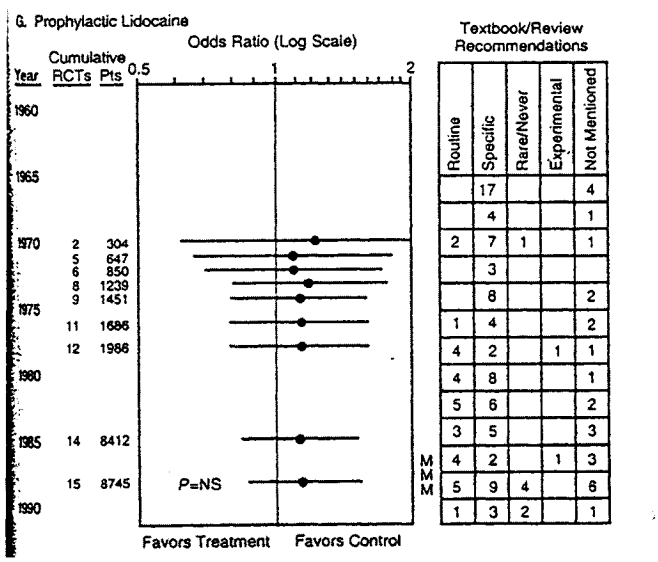


Figure 1-2 Cumulative meta-analysis lidocaine for myocardial infarction

(Antman et al. 1992 (10))

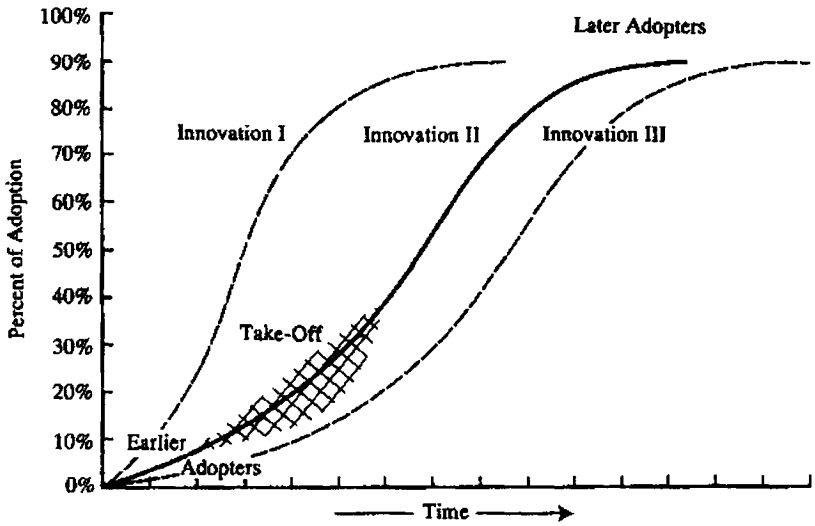


Figure 1-3 S-shaped diffusion curve

(Rogers E., *Diffusion of Innovations* **2005 (13))**

2. Chapter 2 -

The Life Cycle of Evidence in Lung Cancer: Research-Clinical Recommendations Gap

2.1. Introduction

The term **research-practice gap** describes both the failure to incorporate the results of clinical trials results to be incorporated into practice or the premature adoption of unproven treatments **(4).** Thus this gap can be subdivided into the **research-clinical recommendations gap** (the transfer of research into clinical recommendations) and the **clinical recommendations-practice gap** (the transfer of clinical recommendations into practice). This chapter will focus on the former.

Over a decade ago, Antman & Lau examined the temporal relationship between accumulating results from randomized control trials of treatments for myocardial infarction and the recommendations of clinical experts writing review articles and textbooks (5, 10). They utilized the methodology of cumulative meta-analysis (CMA). In CMA, studies are entered sequentially within meta-analytical models (6). For example, Antman and Lau entered studies by publication date and demonstrated the evolution of the available evidence over time. This enabled Antman and Lau to determine if and when

effectiveness of an agent could have been first established by meta-analysis (5, 10).

They found considerable delays between the generation of evidence and when clinical experts made treatment recommendations in line with the new research findings. For example, thrombolytic drugs were not recommended by more than half the review articles and textbooks studied until 13 years after they could have been shown to be effective (Figure 1-1). Furthermore, six years elapsed between when the first meta-analysis showing an impressive reduction in mortality by thrombolytic therapy was published in a commonly read journal and when the majority of experts recommended it for routine or specific use.

Antman's work also revealed an example of a case where a potentially harmful therapy failed to be abandoned and continued to be recommended. For over 25 years, the majority of authors recommended lidocaine for prophylaxis against ventricular fibrillation, yet there was a non-significant increase in mortality associated with the use of lidocaine in the 9 controlled trials conducted between 1970 and 1990 (Figure 1-2).

A CMA has never been performed in the field of oncology. Ford et al. suggest that cancer, more than any other disease, defines state-of-the-art

therapy through clinical trial results (14). However, is the knowledge gained through these clinical trials transferred into practice efficiently?

This study represents a pilot for a Canadian Institutes of Health Research (CIHR) funded project entitled "The Life Cycle of Evidence of Cancer Care". This project's objective is to investigate the relative role of evidence in determining clinical recommendations and practice in cancer control, in particular in lung cancer and breast cancer. This pilot study has chosen to explore the research-clinical recommendations gap in advanced non-small cell lung cancer.

Lung cancer remains the most common cancer diagnosis and cause of cancer related death in North America (20, 21). Non-small cell lung cancer (NSCLC) represents 75-80% of these cases and the majority of patients present with advanced disease defined as incurable disease due to either extensive local, nodal or distant spread (stage III or IV according to the AJCC staging system (22)) for whom the prognosis is palliative.

Palliative chemotherapy has been shown to provide these patients with both a survival and quality of life advantage (23). Meta-analysis of palliative chemotherapeutic agents in treating NSCLC demonstrated that including a platinum agent is the key to providing a survival advantage (24). Despite identifying the use of cisplatin alone or in combination with other

chemotherapeutic agents, response rates remained low (<30%) and incremental survival advantages of are modest (6 weeks). In an ongoing effort to improve on these results, the 1990's saw the emergence of novel chemotherapeutic agents (NCA) such as vinorelbine (Navelbine®, Glaxo-Smith-Kline) and paclitaxel (Taxol®, Bristol-Myers-Squibb), which have been used as single agent and combined with platinum agents in treating advanced NSCLC.

This pilot study uses the methodology of Antman and Lau (5, 10) to document the evolution of the evidence for vinorelbine and paclitaxel, each in combination with a platinum agent for first line advanced NSCLC. We will also review the recommendations over time and compare with the evidence (research-clinical recommendations gap). We have chosen these two drugs based on the fact that both drugs were in the phase II/III portion of their development in the early 1990's and entered the market at least 2 years prior to the end of the study period; choosing them allows future exploration of the research-practice gap. In addition, both drugs successfully captured market share with carboplatin/paclitaxel being the most commonly used platinum-NCA regimen in the US (28), while in Canada and Europe the most commonly used regimen is Cisplatin/Vinorelbine (17, 18).

The objectives include: (1) to perform a systematic review of the evidence for each NCA. (2) to determine the yearly evidence summary by performing a

cumulative meta-analysis of the available data for each NCA, (3) to determine the yearly summary of recommendations and key milestones for each NCA, and (4) to determine the direction and magnitude of the research-clinical recommendations gap.

2.2. Methods

Systematic Review

Searching

A comprehensive search was undertaken to identify relevant trials reported before 2002. The study team established the cut-off of 2002 because they felt that a minimum of 2 years of time was necessary for evidence to be incorporated in recommendations. The search strategy was aimed also to capture bibliometric references for the larger Life Cycles project. The time period for the bibliometric study extended up to 2004.

Electronic databases searched, using the OVID platform, included: MEDLINE (1966-Feb 2004), Embase (1980-Feb 2004), CINAHL (1982-Feb 2004), Biological abs (1990 to December 2004), PreMEDLINE (March 4, 2004). In addition, CENTRAL (4th Quarter 2003), the Cochrane Central Register of Controlled Trials (a bibliographic database of definitive controlled trials identified by the Cochrane Collaboration) was searched. The search strategy for MEDLINE is shown in Appendix B. The same search strategy, with modifications where necessary, was used for searching the other databases.

The search was not restricted by language or publication status (i.e. abstracts were permitted).

These searches were supplemented by hand-searching the proceedings of meetings. Meetings chosen were based on expert opinion, from the Life Cycles project expert advisors and members of the Cancer Care Ontario (CCO) Lung Disease Site committee, as those meetings that had the highest attendance and with the greatest impact in the field of oncology. Meetings searched included American Society of Clinical Oncology Annual Meetings (ASCO) 1987-2002, World Conference on Lung Cancer (WCLC) 1988-2003, American Association for Cancer Research (AACR) 1987-2002, European Cancer Conference (ECCO) 1991-3003, and European Society of Medical Oncology (ESMO) 1990-2002.

Once an index publication (either a conference abstract or peer reviewed publication) was identified for a trial, we conducted further electronic searches on the lead authors' names to identify all publications related to the trial. However, if a search only identified a full publication for a trial, or conversely only an abstract, and the search by lead author's name did not produce further publications, then further electronic searches by all authors other than lead author was performed.

Inclusion criteria

Participants: The study population included patients with advanced NSCLC (stage III and IV) according to the AJCC staging system (22) (see Appendix A). Based on current standards of care, stage IIIA patients typically undergo curative therapy either with surgery and/or with combined chemotherapy and radiation. Initially, this population was to be excluded. However, a preliminary review of the search results revealed that early on in the study time period these patients may have been included in studies of palliative therapies. After consultation with the Life Cycles project expert panel, the group felt it be appropriate for these patients to be included for the respective time period.

Intervention: The study examined the use of vinorelbine or paclitaxel in combination with a platinum chemotherapeutic agent (cisplatin or carboplatin). The use of NCA as palliative chemotherapy can either be as a single agent or in combination with other agents. When an NCA is studied as a single agent, typically the comparator is best supportive care (BSC) and the study establishes activity of the agent and its efficacy. However, optimal therapy for advanced NSCLC would involve the use of a platinum agent alone or in combination with another agent (24). This study focused on NCA-platinum combination therapy versus platinum-based control arms to establish the incremental benefit of adding the NCA to a platinum agent. The

intervention arm needed to have contained a platinum agent and either vinorelbine or paclitaxel. Intervention arms with 3 or more chemotherapeutic agents were excluded as no study has shown a superior survival advantage of these regimens over 2 drug combinations that include a platinum agent (29).

Study design: For studies to be eligible, they must be randomised control trials (phase II or III). The control arm must also be a standard platinum based chemotherapy regimen. In addition, no NCA introduced since 1990 can be included in the control arm as the study is looking for incremental benefit over agents present prior to 1990 and recent data has shown equivalence of NCAs introduced since 1990 (30, 31).

As the intent of the trial must be palliative, neoadjuvant or adjuvant chemotherapy trials were excluded. In order to avoid confounding, trials of chemotherapy given in combination with radical radiotherapy (> 30 cGray total dose) were also excluded (palliative radiotherapy would be allowed). Trials comparing dose levels of the NCA, or NCA dose frequency without standard control arm as mentioned previously were excluded. Drug sequencing or cross-over trials were also excluded, as these types of studies did not examine the incremental benefit of the NCA.

Outcome: The primary outcome of interest was survival. Therefore, only randomised controlled trials (phase II or III) that report survival data were eligible. The preferred measure of survival was the hazard ratio (HR). Other endpoints of clinical interest were median survival and response rate.

Screening and assessment of studies

Trials were independently selected for inclusion by two reviewers (NR & MN or SM). Differences in opinion were resolved by consensus reached after discussion.

Data abstraction

Data were abstracted independently by two reviewers (NR & MN or SM) using a structured form (Appendix B). The form was designed to capture information on: details of the trial (first author, number of centres, sources of funding, study design, sample size); patient characteristics (age, stage of disease, performance status, and prior treatment status); quality criteria (using the Jadad scale (32) and documentation of whether allocation concealment was performed); and details of the intervention and outcomes (dosage, frequency of administration, toxicity, response rate, and survival rate). Differences in opinion were resolved by consensus reached after discussion.

Data Analysis

CMA methods as described by Lau were used (6). At each point in time, available trial references (abstract or full publication) were entered sequentially by date of publication into a random effects meta-analysis to establish the cumulative evidence available.

The preferred outcome statistic from trial references for incorporation into the meta-analysis was a reported HR. As these studies extended back more than a decade, it was possible that all studies did not report this value. Therefore, a secondary calculation of the hazard ratio was planned using the published stratified survival curves. If this was not possible, then a t-test was performed on the difference in median survivals between comparison arms of each study which approximates a random effects model of meta-analysis (33). Calculations were performed using R software version 2.0.1 (The R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). Programming code for each NCA can be seen in Appendices A & G.

Pooled summary estimates were calculated for each year that new or updated evidence was available (Appendices H & I). As updated trial abstract or full publication results appeared, previous data of the same trial were removed. Pooled summary values were then plotted chronologically in a Forrest plot.

Search for Key Milestones

In addition to documenting recommendations (CPG & textbooks), manual electronic searches were performed to determine the following key milestones for each NCA: first governmental approved indication for any site and first indication for NSCLC (United States Food and Drug Authority [FDA] approval [http://www.accessdata.fda.gov/scripts/cder/drugsatfda], Health Canada Notice of Compliance [NOC] [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index_e.html]), and first provincial funding by Cancer Care Ontario (CCO) (personal correspondence with New Drug Funding Program [NDFP] office, CCO, Toronto, Ontario, Canada) . CCO provincial funding of regional cancer centers is through the NDFP for NCA that have entered the market since 1995. Drugs need to be listed as eligible by the program to be reimbursed, otherwise regional centers must use local budgets deemed for older agents to fund newer agents.

Search for Recommendations

As many clinical practice guidelines (CPG) are never published in the peer-reviewed journals (34), we also electronically searched the US National Guidelines Clearinghouse and known cancer care guideline developer websites (Appendix L). Once we identified guidelines, we obtained all previous versions of guidelines. If not available electronically, we contacted authors.

We also retrieved current and previous editions of major general and oncological textbooks (as determined by expert panel from the Life Cycles project, CCO Lung Disease Site Group and The Ottawa Hospital library services) published since 1990 (Appendix K). Hardcopies were obtained from The Ottawa Hospital, University of Ottawa, and Canada Institute for Scientific and Technical Information (CISTI).

Reviewers (MN and NR) independently classified the recommendations of the CPG and textbooks. The recommendations for each NCA were classified either as: (i) Not mentioned (NM); (ii) Mentioned but reported as experimental agent (E); (iii) Indicated for 2^{nd} or greater line therapy (I); or (iv) Standard therapy as 1^{st} line option (S). Differences were reconciled by consensus and no adjudication was required.

Following the methodology of Antman & Lau (5, 10), if more than half of the recommendations for that year supported the use of the NCA either as indicated (I) or standard (S), then it was deemed that the NCA had become recommended therapy.

2.3. Results

Search results

In total, 4557 references were obtained for the Life Cycles project of NCAs in advanced NSCLC (4341 database search, 216 hand search). After initial abstract screening and follow-up detailed screening (Figure 2-1), there remained 203 potentially eligible references. A full eligibility review of these remaining references resulted in 20 references for vinorelbine representing six RCTs and 16 references for paclitaxel representing four RCTs (see Appendices D & E). It should be noted that one reference (35) had three arms with both vinorelbine and paclitaxel in a respective experimental arm and therefore the trial applied to both NCA systematic reviews.

Vinorelbine results

Trial demographics are summarized in Table 2-1. There were six trials with 1450 patients enrolled. Five trials reported the phase of the study: one phase II (36) and four phase III. Only one trial was non-European and was based in the USA (37). The mean number of patients per trial was 242 (range 97-432). Median ages and age ranges were similar across the studies. Two trials included stage IIIA patients (25, 35). Two trials were published in abstract form only (35, 38).

Evidence timelines and data summary are seen in Table 2-2. All six trials reported response rates with five trials reporting improved response rates for

vinorelbine but only three reported p values (two were statistically significant (25, 37)). The difference seen in the one trial that did not report improved response rates for vinorelbine was not statistically significant. All trials reported median survival with five trials reporting improved survival for vinorelbine. However, only one of these trials reported a HR (39). The HR for this trial was statistically significant. Of the remaining four trials favouring vinorelbine, only two reported p values on the differences in median survival and neither was statistically significant. The trial that favoured the control for median survival did not report a p value (36). Three of six trials published survival curves but none were presented in stratified format.

The first trial to publish survival data was by Le Chevalier et al. in 1994 (25). This study enrolled 406 patients and was the second largest trial of vinorelbine in combination with platinum. It was based in France and was sponsored by a French pharmaceutical company Pierre Fabre. It was a three arm trial comparing cisplatin-vinorelbine versus single agent vinorelbine versus cisplatin–vindesine (control arm). The first publication with survival data was the full publication in 1994. However, an abstract without survival data was reported at the ASCO meeting in 1992 and it is unknown whether survival data was presented at the meeting. Survival advantage was found for cisplatin-vinorelbine versus the cisplatinum-vindesine arm with an eight week incremental survival benefit resulting in a hazard ratio of 1.4 (p=0.006).

Jaddad score for this trial was three and allocation concealment was performed.

In the same year (1994), vinorelbine received both US FDA and Health Canada NOC. This was the first ever FDA approval and Health Canada NOC for vinorelbine allowing it on to the US and Canadian markets. FDA public documents (www.accessdata.fda.gov/scripts/cder/onctools) reveal the advisory committee voted 6-4 in favour of approval for single agent vinorelbine for treatment of stage IV NSCLC with adequate performance status. This decision was based on one phase III study of single agent vinorelbine versus 5-fluorouracil and leucovorin demonstrating a significant survival advantage (40). The committee voted 10-0 in favour of approval for combination (with cisplatin) for fully ambulatory patients with advanced NSCLC. This was based solely on the Le Chevalier trial (25).

Two years later in 1996, Wozniak et al. were the next to report survival data in abstract form at the ASCO meeting (41). This trial was based in the USA and coordinated through the Southwest Oncology Group (SWOG) and was sponsored by the pharmaceutical company Glaxo-Wellcome (now Glaxo-Smith-Kline). The trial enrolled 432 patients and was the largest trial of vinorelbine in combination with cisplatin (25). However, this trial had only two arms, compared to three arms in the LeChevalier trial. It was the only trial to use a single agent cisplatin control arm. The trial demonstrated improved

response rates and an eight week incremental survival benefit favouring vinorelbine, with both results being statistically significant. The Jadad score for this trial was two and allocation concealment was performed.

Also in 1996, Cancer Care Ontario (CCO) published their guideline indicating vinorelbine as the recommended standard of care for first line therapy. A review of the guideline and textbook recommendations indicated that 1996 was the year where more than half of the new recommendations were in favour of vinorelbine as a first line option.

In 1997, ASCO guidelines also recommended vinorelbine as a standard therapy (42). As well, CCO granted funding through the CCO New Drug Funding Program to regional cancer centers to provide vinorelbine for patients with advanced NSCLC.

In 1998 two European trials were reported. Baldini et al. reported the only randomized phase II trial and the only trial using the combination of carboplatin-vinorelbine (36). Based in Italy, any sponsorship by a pharmaceutical company was not reported. The trial enrolled 97 patients and was therefore the smallest trial. The authors reported slightly better response rates but median survival was worse with vinorelbine (two month incremental detriment). No HR or p value was reported. The Jadad score for this trial was three but allocation concealment was not reported.

Bilaceroglu et al. reported a phase III three arm trial in abstract form with cisplatin-vinorelbine versus cisplatin-paclitaxel versus cisplatin-etoposide (35). This trial was based in Turkey and any sponsorship by a pharmaceutical company was not reported. The trial enrolled 144 patients total in the vinorelbine and control arm (218 patients total in all three arms). The authors reported an improved response rate for vinorelbine but this was not statistically significant. They also reported a three month incremental benefit for vinorelbine but no HR or p values were reported. This study was only reported in abstract form (i.e. never published as a full text document in a peer reviewed journal). The Jadad score for this trial was one and allocation concealment was not reported.

In 2002, eight years after the LeChevalier report, the results of two more trials were reported. Both trials were from Europe. Melo et al. reported a phase III trial in abstract form from the ASCO meeting of cisplatin-vinorelbine versus mitomycin-vindesine-cisplatin (38). This trial was based in Portugal and any sponsorship by a pharmaceutical company was not reported. The trial enrolled 124 patients. The authors reported improved response rates but no p value was reported. They also reported median survival improvement with the vinorelbine arm having an 11 week incremental benefit, but no HR or p value were presented. This study was only reported in abstract form. The Jadad score for this trial was one and allocation concealment was performed..

In a full publication, Gebbia et al. reported a phase III trial of cisplatinum-vinorelbine versus mitomycin-vindesine-cisplatin (43). This trial was based in Italy and any sponsorship by a pharmaceutical company was not reported. The trial enrolled 247 patients. The authors reported slightly worse response rates for vinorelbine but both arms had high response rates and the difference was not statistically significant. Survival data favoured the vinorelbine arm with a six week incremental benefit, but the difference failed to reach statistical significance with a p value of 0.898. The Jadad score for this trial was two and allocation concealment was performed.

In summary, the mean time from end of accrual to first publication with data (abstract or full publication) was 31.8 months (range 11-55). Mean time from end of accrual to first full publication was 40.5 months (range 27-55) with 2 trials never being fully published. The quality of the trial reporting as measured by Jadad scores generally reflected the better quality of larger trials (except for Baldini). Most importantly, poorer quality trials and reporting was noted if trials were not fully published in peer reviewed journals.

Due to the lack of reporting of either HR or appropriate survival curves, we utilized a t-test on the difference in median survivals between comparison arms of each study which approximates a random effects model of meta-analysis (33).

The CMA for vinorelbine is shown in Figure 2-2. The CMA failed to demonstrate with statistical significance any point in time where the evidence favoured the use of a platinum-vinorelbine combination over platinum control regimens. All summary pooled points trended towards favouring the platinum-vinorelbine combinations and final pooled median survival advantage was 3.9 weeks (95% CI -2.29, 10.09).

Paclitaxel results

Trial demographics are summarized in Table 2-3. The eight references represented four trials. All trials were phase III and all used cisplatin-paclitaxel in the experimental arm. Only one trial was non-European and was based in the USA (39). There were 1379 patients enrolled in clinical trials for paclitaxel. The mean number of patients per trial was 344 (range148-599). Median ages and age ranges were similar across the studies. Two trials reported including stage IIIA patients. One trial was published in abstract form only (35).

Evidence timelines and data summary are seen in Table 2-4. All trials reported improved response rates with paclitaxel with statistically significant p values. No trials reported a HR. Two trials reported improved median survival for the paclitaxel arm (35, 39); only one reported a p value and it was statistically significant (39). Two trials reported worse median survival for the

paclitaxel arm, and both reported p values, which were not statistically significant. Two of four trials published survival curves but neither were in stratified format.

The first trial to publish survival data was Bonomi et al. in 1997 (44). This was in abstract form and was presented at the ASCO meeting. This was a 3 arm study with paclitaxel in both experimental arms comparing cisplatin-paclitaxel (standard dose & high dose) versus cisplatin–etoposide. The trial was based in the USA and coordinated through the Eastern Cooperative Group (ECOG). It was sponsored by the US National Cancer Institute. This was the largest paclitaxel trial, enrolling 599 patients. Abstract data was published with stage IIIb and IV results presented separately. The text of the 1997 abstract suggests survival data was presented at the ASCO meeting in 1996, but review of the abstract from 1996 revealed no survival data suggesting it was presented orally. In 1997, using an analysis that combined the two experimental arms, results showed survival advantages of 5.1 months and 2.9 months for either stage IIIb or IV patients respectively, but neither result was statistically significant. No response rate data was published in 1997. Full publication of this trial occurred in 2000 showing an overall survival advantage of 11 weeks for both stage IIIb and IV combined but again this was not statistically significant unless both paclitaxel arms were combined (p=0.048). The Jadad score for this trial was two and allocation concealment was not performed.

In 1996, CCO published their guideline for the management of advanced NSCLC and no mention was made of paclitaxel.

In 1997, Giaccone et al. published an abstract at the ASCO meeting (45). This was a European trial based in the Netherlands and coordinated through the European Organization for Research and Treatment of Cancer (EORTC) and was sponsored by the pharmaceutical company Bristol-Myers-Squibb. They reported improved response rates for paclitaxel, but a one month incremental detrimental effect for the experimental arm. The survival difference was not statistically significant (p=0.971). The Jadad score for this trial was two (note: minimization allocation was performed) but allocation concealment was not reported.

In the same year, 1997, ASCO published their guideline on the management of NSCLC and recommended paclitaxel as standard of care for first line treatment of advanced NSCLC.

In 1998, Gatzemeier et al. reported in abstract form at the ASCO meeting a trial of cisplatin paclitaxel versus paclitaxel (46). This was the only trial to use single agent cisplatin as the control arm. This trial was based in Germany and was sponsored by the pharmaceutical company Bristol-Myers-Squibb. The trial enrolled 414 patients and was the largest European trial. The authors

reported improved response rates for paclitaxel, which were statistically significant. Median survival was worse (two month incremental detriment) for the paclitaxel arm but this was not statistically significant. The Jadad score for this trial was one (note: minimization allocation was performed) and allocation concealment was performed.

Also in 1998, another European trial by Bilaceroglu et al. was reported in abstract form with cisplatin-vinorelbine versus cisplatin-paclitaxel versus cisplatin-etoposide (previously described in the vinorelbine summary) (35). The trial enrolled 148 patients total in the paclitaxel and control arm (218 patients total in all three arms). The authors reported improved a response rate for paclitaxel, which was statistically significant. They also reported a 6.5 month incremental benefit for paclitaxel but no HR or p value were reported. This study was only reported in abstract form. The Jadad score for this trial was one and allocation concealment was not reported.

In 1998, the US FDA granted approval of paclitaxel for the indication of NSCLC. This was largely based on the marginally positive result of the Bonomi trial. FDA records reveal that paclitaxel was approved by a vote of 5-2 with reviewers using not only median survival data but also one year survival, time to progression and quality of life data (47).

A review of the guideline and textbook recommendations indicated that the year 2000 was when more than half of the new recommendations were in favour of paclitaxel as a first line option.

Only in 2002 did Health Canada grant NOC for paclitaxel, much later than FDA approval. However, it should be noted that the drug was already on the market for an ovarian indication since 1992 and available for "off label" use (used for a condition which is not listed as an indication on the label) by physicians. CCO funding for paclitaxel did not occur until 2003, six years after FDA approval and 2 years after NOC.

In summary, the mean time from end of accrual to first publication with data (abstract or full publication) was 32.6 months (range 15-29). Mean time from end of accrual to first full publication was 48.3 months (range 28-62) with two trials never being fully published. The quality of reporting was generally good with the exception of one smaller trial (35) that was only reported in abstract form.

Due to the lack of reporting of either HR or appropriate survival curves, we utilized a t-test on the difference in median survivals between comparison arms of each study which approximates a random effects model of meta-analysis (33).

CMA for paclitaxel shown in Figure 2-3. Similar to vinorelbine, the CMA failed to demonstrate with statistical significance any point in time where the evidence favoured the use of a platinum-paclitaxel combination over platinum control regimens. All summary pooled points trended towards favouring the platinum-paclitaxel combination and final pooled median survival advantage for paclitaxel was 3.6 weeks (95% CI –6.25, 13.51).

From a clinical standpoint for both NCAs, all studies were homogeneous with platinum based chemotherapy in both the experimental and control arms and all trials had similar mean ages. Due to the small number of trials for each NCA it was impossible to perform tests for heterogeneity in accordance with the Cochrane collaboration recommendations(48).

Recommendations

Results of coding of recommendations & key milestones are presented in Figure 2-2 and Figure 2-3. General recommendations, as determined by more than half of new CPGs or textbooks in a given year recommending a therapy as either standard therapy or an indication, supported the use of vinorelbine in 1996 and paclitaxel in 2000. As the CMA did not determine there was sufficient evidence to warrant recommendations for either NCA, the research-clinical recommendations gap cannot be quantified for either NCA.

2.4. Discussion

Statement of principal findings

This study documented the evolution of evidence, recommendations and key milestones of two NCA for the care of patients with advanced NSCLC. For vinorelbine, the review revealed two early large RCTs with relatively large magnitudes of benefit that facilitated early governmental drug approval and funding. The majority of CPG and textbooks began to recommend the use of vinorelbine at the same time. However, of the four smaller studies that followed, magnitudes of benefit were less (or in one case inferior). The CMA performed in this study was unable to determine with statistical significance sufficient evidence to warrant the recommendations.

For paclitaxel, this study also revealed that the result of one early large RCT, with marginally significant results, was the basis for an ASCO guideline recommendation and facilitated US governmental approval. This was the only trial to demonstrate a statistically significant incremental benefit of a platinum-paclitaxel regimen out of four trials. However, the majority of CPG and textbooks did not begin to recommend the use of paclitaxel until 2000 and Health Canada did not grant NOC until 2002. Similar to vinorelbine, the CMA performed in this study was unable to demonstrate with statistical significance sufficient evidence to warrant the recommendations.

In the absence of sufficient evidence to recommend therapy, it would appear that research-clinical recommendation gap was not quantifiable. Yet it would appear there is a gap as the recommendations do not reflect the available evidence. The question is then are the recommendations appropriate or not? If we make the assumption that the first large trial with statistically significant results is sufficient for evidence, then the research-recommendation gap for vinorelbine would be less than 2 years and paclitaxel would be and less than 3 years. Further trials could either solidify or contradict the recommendations, which would then make the research-clinical recommendation gap either premature or inappropriate. However, this is unlikely, as both these NCA soon became part of the control regimens for subsequent trials.

This study has demonstrated that in the treatment of advanced NSCLC, guideline developers and textbook authors are making early recommendations based on limited evidence. This may reflect that treatment options for this population are suboptimal and that marginal gains or secondary endpoints such as time to progression, response rate and quality of life are considerations.

Strengths and weaknesses of the study

This study has provided a unique comprehensive review of the both the clinical evidence and concomitant recommendations over time. It suggests that in lung cancer treatment the research-clinical recommendation gap is much shorter than previously described in other diseases.

Limitations of this study are largely due to the limited clinical evidence available and the poor quality of reporting, especially in abstracts. Due to variable outcome reporting, the study was required to perform t-tests on the difference in median survivals between comparison arms of each study, which approximates a random effects model of meta-analysis. This technique is a considered a conservative technique of meta-analysis which reduces the risk of type I error. This technique also does not take into account differences in study size or statistical significance of results. Therefore, better reporting of results would have allowed the use of more traditional methods of meta-analysis and possibly provided a statistically significant result.

Strengths and weaknesses in relation to other studies

This study has provided an interesting comparison to the Antman & Lau study. As compared to cardiology and the evidence for thrombolytic therapy, there is a relative paucity of trials for NCA. In order for Antman & Lau to demonstrate evidence in favour of thrombolytics, their cumulative meta-analysis required over 2500 patients. Meanwhile, this study has demonstrated that the entire pool of evidence for each NCA is based on less than 1500 patients per drug.

However, despite the lack of research evidence, the study was able to demonstrate that the field of oncology is willing to act early on clinical results as opposed to cardiology that can require large amounts of clinical results prior to recommending change in practice.

Meaning of the study: possible mechanisms and implications for clinicians or policymakers

Decision makers at both the research and recommendation levels need to be aware of the relative lack of satisfactory evidence. Better reporting may ameliorate the problem but the need for more trials may necessary.

Guideline developers should also be more rigorous in development of their recommendations to avoid the widespread premature adoption of drugs that may provide no incremental benefit.

Unanswered questions and future research

This study addressed the question of the incremental benefit of vinorelbine and paclitaxel in combination with cisplatin on survival. There appears to be a disconnect between the available data and current recommendations, and possibly either a premature or inappropriately reversed research-clinical recommendation gap. The clinical recommendations-practice gap, the second part of the research to practice continuum, needs to be explored.

Figures & Tables

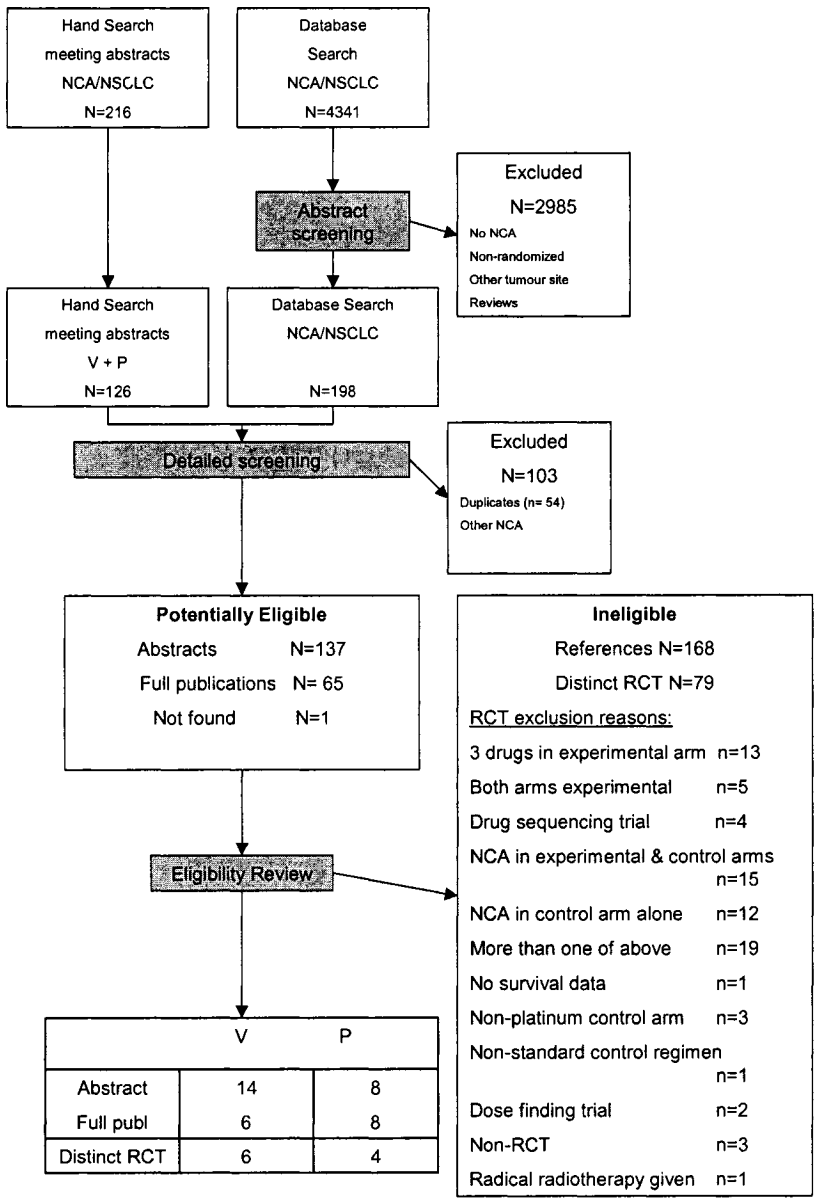


Figure 2-1 Systematic review search results

NCA = Novel Chemotherapeutic Agent
NSCLC = Non Small Cell Lung Cancer
RCT = Randomized Controlled Trial
P = Paclitaxel
V = Vinorelbine

Table 2-1 Vinorelbine: summary of studies

Trial	Experimental	Control	Phase	Lead country	Multicenter	Pharma-ceutical sponsor	# Pts	Mean age (Range)	Stage IIIA Patients	Jadad score	Allocation Concealment
Le Chevalier (25)	vinorelbine-cisplatin	vindesine-cisplatin	3	France	Y	Y (Pierre Fabre)	406	59 (NR)	Y	3	Y
Wozniak (37)	vinorelbine-cisplatin	cisplatin	3	USA	Y	Y (Glaxo-Wellcome)	432	63 (33-84)	N	2	Y
Baldini (36)	carboplatin-vinorelbine	cisplatin-vindesine-mitomycin	2	Italy	Y	NR	97	62 (37-72)	N	3	NR
Bilaceroglu (35)	vinorelbine-cisplatin	etoposide-cisplatin	3	Turkey	NR	NR	144	NR	Y	1	NR
Melo (38)	vinorelbine-cisplatin	mitomycin-vinblastine-cisplatin	3	Portugal	NR	NR	124	NR	NR	1	Y
Gebbia (43)	vinorelbine-cisplatin	cisplatin-vindesine-mitomycin	NR	Italy	Y	NR	247	61 (37-75)	N	2	Y

NR = not reported

Table 2-2 Vinorelbine: Summary of data

Author	Experimental	Control	# references with survival data	Initial accrual (M/Y)	End accrual (M/Y)	First abstract with survival data (M/Y)	First full publ. (M/Y)	RR Exp/ Control (%)	RR P value	median survival Exp/ Control (weeks)	MS p value	HR	HR p value
Le Chevalier (25)	vinorelbine-cisplatin	vindesine-cisplatin	2	Jun 1989	May 1991	-	Feb1994	30/19	0.02	40/32	0.085	1.4	0.006
Wozniak (41)	vinorelbine-cisplatin	cisplatin	3	Nov 1993	Apr 1995	May 1996	Jul 1998	54/25	0.0002	32/24	0.0018	NR	NR
Baldini (36)	carboplatin-vinorelbine	cisplatin-vindesine-mitomycin	1	Apr 1993	Jul 1994	-	Jun 1998	17/14	NR	31.6/33.6	NR	NR	NR
Bilaceroglu (36)	vinorelbine-cisplatin	etoposide-cisplatin	1	NR	NR	Sept 1998	-	42/27	0.094	36.5/33.5	NR	NR	NR
Melo (38)	vinorelbine-cisplatin	mitomycin-vinblastine-cisplatin	1	Jun1998	Jun 2001	May 2002	-	37/27	NR	36/25.6	NR	NR	NR
Gebbia (43)	vinorelbine-cisplatin	cisplatin-vindesine-mitomycin	1	Jan 1996	Jan 1998	-	Aug 2002	39/42	0.13	27/21	0.898	NR	NR

RR = response rate, MS = median survival, HR = Hazard Ratio
Full pub = full text publication, NR = not reported

Table 2-3 Paclitaxel: summary of studies

Author	Experimental	Control	Phase	Lead country	Multicenter	Pharma-ceutical sponsor	# Pts	Mean age (Range)	Stage IIIA Pts	Jadad score	Allocation Concealment
Bonomi (39)	cisplatin-paclitaxel	cisplatin-etoposide	3	USA	Y	NR	599	61.8 (NR)	Y	2	N
Giaccone (45)	cisplatin-paclitaxel	cisplatin-teniposide	3	Netherlands	Y	Y	332	58.5 (28-75)	N	2	NR
Bilaceroglu (45)	cisplatin-paclitaxel	cisplatin-etoposide	3	Turkey	NR	NR	148	NR	Y	1	NR
Gatzemeier (46)	cisplatin-paclitaxel	cisplatin	3	Germany	NR	Y	414	60 (32-75)	N	1	Y

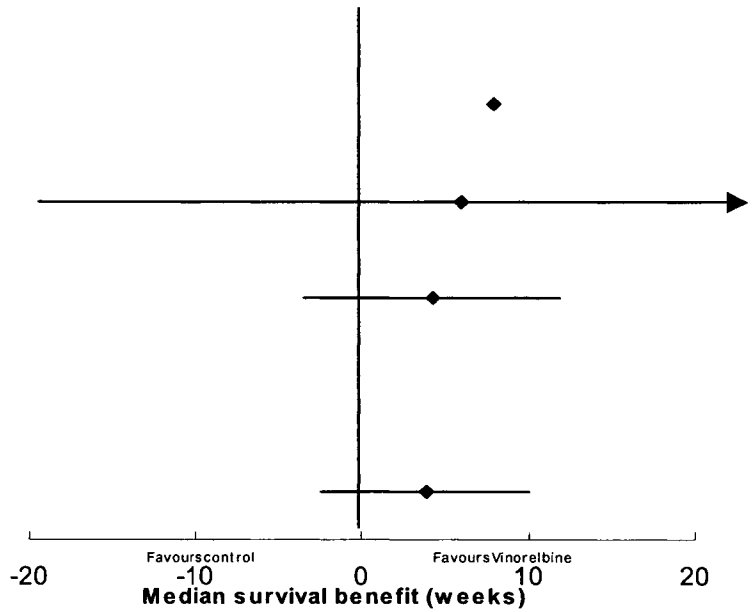
NR = not reported

Table 2-4 Paclitaxel: summary of data

Author (references)	Experimental	Control	# ref with survival data	Initial accrual (M/Y)	End accrual (M/Y)	First abstract with survival data (M/Y)	First full pub (M/Y)	RR Exp/ Control	RR P value	median survival Exp/ Control (weeks)	MS p value	HR	HR p value
Bonomi (39)	cisplatin-paclitaxel	cisplatin-etoposide	1	Aug 1993	Dec 1994	May 1997	Feb 2000	28/12	<0.001	44/33	0.097	NR	NR
Giaccone (45)	cisplatin-paclitaxel	cisplatin-teniposide	2	Jul 1993	Feb1996	May 1997	Jun 1998	41/28	0.018	41/42	0.971	NR	NR
Bilaceroglu (35)	cisplatin-paclitaxel	cisplatin-etoposide	1	NR	NR	Sep 1998	NR	47/27	0.036	40/33.5	NR	NR	NR
Gatzemeier (46)	cisplatin-paclitaxel	cisplatin	3	Jan1995	Apr 1996	Apr 1998	Oct 2000	24/16	0.047	35/37	0.862	0.981	NR

RR = response rate, MS = median survival, HR = Hazard Ratio
Full pub = Full text publication

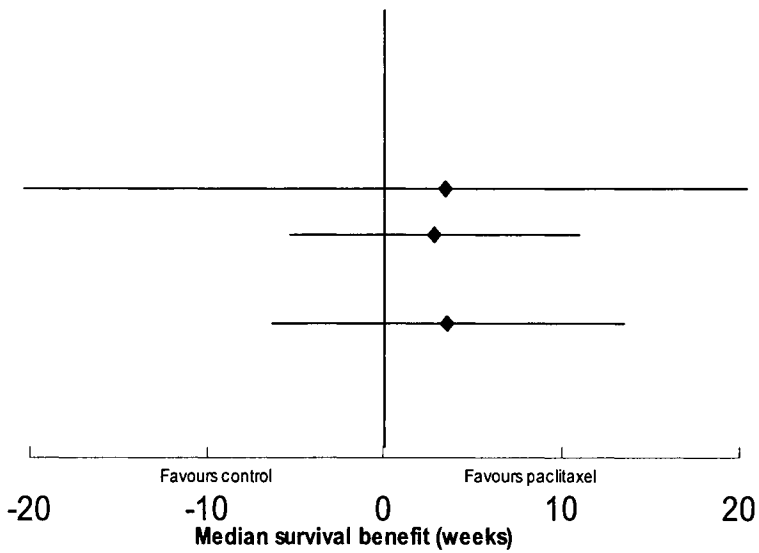
Figure 2-2 Vinorelbine: cumulative meta-analysis and summary of recommendations & key milestones



Year	Studies				Textbook & CPG recommendations				Key Milestones
	cumul # pts	Active A	Active P	cumul totals A/P	NM	E	I	S	
1992					1				
1993					1	2			
1994	406		1	1/0	1	2		1	1st FDA approval NOC (NSCLC)
1995									
1996	838	1	1	2/1	2			2	CCO guideline (S)
1997						1		3	ASCO guid. (S), CCO funding
1998	1153	1	3	3/3	1	1		1	
1999								1	
2000								2	
2001					1			4	
2002	1524	2	4	5/4	3			1	

Cumul = cumulative
A = abstract
P = full text publication
NM = not mentioned
E: Mentioned but reported as experimental agent
I = Indicated as second line or greater therapy
S = Standard first line therapy
FDA = US Food and Drug administration
NOC = Health Canada Notice of Compliance
CCO = Cancer Care Ontario

Figure 2-3 Paclitaxel: cumulative meta-analysis and summary of recommendations & key milestones



Year	Studies				Textbook & CPG recommendations				Key Milestones
	cumul # pts	Active A	Active P	cumul totals (A/P)	NM	E	I	S	
1992					2				1st FDA & 1st NOC (ovarian)
1993					1	2			
1994						1			
1995						2			
1996					2	1		2	CCO guideline (NM)
1997	817	2		2/0		2	1	1	ASCO guideline (S)
1998	1379	3	1	3/1		2		1	FDA approval NSCLC
1999								1	
2000	1379	1	3		1		1	1	
2001							1	1	
2002					2			1	NOC NSCLC

Cumul = cumulative
A = abstract
P = full text publication
NM = not mentioned
E: Mentioned but reported as experimental agent
I = Indicated as second line or greater therapy
S = Standard first line therapy
FDA = US Food and Drug administration
NOC = Health Canada Notice of Compliance
CCO = Cancer Care Ontario

3. Chapter 3 – The Life Cycle of Evidence in Lung Cancer: Clinical Recommendations-Practice Gap

3.1. Introduction

The failure of the results of clinical trials to be incorporated into practice or the premature adoption of unproven treatments is sometimes referred to as the **research-practice gap** (4). To better understand how this phenomenon might occur, the research-practice gap can be subdivided into the **research-clinical recommendations gap** (the transfer of research into clinical recommendations) and the **clinical recommendations-practice gap** (the transfer of clinical recommendations into practice).

The research-clinical recommendation gap has previously been explored in cardiology using cumulative meta-analysis (CMA) (5, 10). In chapter two, the first part of a pilot study for the Life Cycles of Evidence in Cancer Care project examined the research-clinical recommendation gap in lung cancer.

Lung cancer remains the most common cancer diagnosis and cause of cancer related death in North America (20, 21). Non-small cell lung cancer (NSCLC) represents 75-80% of these cases and the majority of patients present with advanced disease (stage III or IV according to the AJCC staging

system (22)) for whom the prognosis is palliative. Palliative chemotherapy has been shown to provide these patients with both a survival and quality of life advantage (23). Meta-analysis of palliative chemotherapeutic agents in treating NSCLC demonstrated that including a platinum agent is the key to providing a survival advantage (24). The 1990's saw the emergence of novel chemotherapeutic agents (NCAs) such as vinorelbine and paclitaxel with single agent activity against NSCLC. However what is the incremental benefit of adding either NCA to a platinum agent in the treatment of advanced NSCLC?

The first phase of the pilot study (see Chapter 2) used a systematic review to demonstrate that there was limited evidence for both NCAs in this specific indication. CMA methods also showed there was insufficient evidence for clinical recommendations for the use of either NCA for the above indication. Nevertheless, both drugs were recommended for the treatment of advanced NSCLC by a majority of new guidelines and textbooks within a relatively short period of time after the results of the first large trials demonstrating statistically significant benefits were published. This suggests a short and either premature or inappropriate research-clinical recommendations gap exists. This chapter will study the remainder of the research-practice continuum for these two NCAs in order to provide the first complete picture of the evidence-practice gap in lung cancer. This study will document the

adoption and utilization patterns of physicians within the Ontario regional cancer centre system coordinated by Cancer Care Ontario (CCO).

The objective of this study was to determine: (1) the level of adoption of each NCA by physicians, (2) the rate of adoption by Ontario physicians, (3) the pattern of adoption when plotted over time, (4) the regional differences in adoption rates, and (5) the timing of adoption in relation to evidence, recommendations and key milestones.

3.2. Methods

Chapter 2 reported on the methods for determining the evidence, recommendations and key milestones for both platinum-NCA combinations. In summary, a systematic review of evidence for vinorelbine and paclitaxel was performed using database and hand searches of meeting proceedings to determine the available evidence up until 2002. This search identified six randomized controlled trials (RCT) for vinorelbine and four RCTs for paclitaxel. Subsequently, a CMA was performed on the available data to determine the timing of sufficient evidence for clinical recommendations for or against the NCA. Unfortunately data were limited and no statistically significant result favouring either the intervention (NCA+platinum) or control was obtained. In addition, a comprehensive search for clinical practice guidelines (CPG) and textbooks from the period 1990-2002 was performed and recommendations were recorded. It was determined that more than half

of CPGs and textbooks recommended the use of vinorelbine by 1996 and paclitaxel by 2000. Finally, key milestones for US and Canadian drug approval, as well as Ontario drug funding were found. Results of the CMA, review of recommendations and key milestones can be seen in Figure 2-2 & Figure 2-3

For the purpose of this study, physician use of each NCA was determined using the CCO Oncology Patient Information System (OPIS) database. The OPIS database captures physician drug use through the electronic order entry of chemotherapy orders by physicians.

The OPIS system database was only able to provide us with comprehensive data from 1997 to 2004, which corresponded to the introduction of the OPIS 2000 interface for physician computer entry of chemotherapy orders. Of the nine regional cancer centres that were included in this database, data for only six centres spanned the entire spectrum from 1997-2004. As 1997 will, by default, represent the initial adoption year for many physicians who began prescribing in 1997 or earlier, this will likely overestimate adoption rates for 1997 alone. Introducing centres starting to use the OPIS 2000 interface at later dates into the analysis will thus create repeated years of high adoption throughout the analysis and make the data impossible to interpret. Therefore the analysis was limited to the six centres with data for the whole study

period. The six centres represented both large and small centers from a variety of different geographic locations.

This study wished to identify only physicians who treat lung cancer by prescribing chemotherapy. Therefore, physicians must have prescribed an intravenous systemic chemotherapy for lung cancer to qualify for entry into the analysis. Physician identity, except for center of practice, was made anonymous by CCO prior to analysis.

Yearly (calendar) prescription data for NCA vinorelbine and paclitaxel were obtained for each physician prescribing to patients with advanced lung cancer. Due to lack of staging information in the database, a surrogate marker to identify patients with advanced stage was sought. Physicians are required to enter the intent of treatment as either palliative versus curative or adjuvant. Therefore a response of palliative intent was used as a surrogate marker of advanced disease. Because the data provided did not link the NCA to a regimen, all usage was assumed to be first line therapy in combination with a platinum agent. In addition, the database does not differentiate between small cell lung cancer (SCLC) and NSCLC. However, treatment with these NCA is not standard therapy for SCLC, and thus all prescriptions were assumed to be for NSCLC.

The study aimed to determine the number of patients started on the drug, not the total number of prescriptions of the drug. In order to avoid double counting from repeated prescriptions to a single patient, data extraction was limited to the first prescription to each individual patient (new prescriptions).

Individual physician data was analyzed using Microsoft Excel 2000 Version 9.0.4402 SR-1(Microsoft Corporation 1999) to identify for each physician: (1) the year of first ever prescription by the physician in the database for advanced lung cancer (start year); (2) years of active prescribing for advanced lung cancer; (3) the year of first new prescription of each NCA (adoption year); and, (4) yearly total of new prescriptions of each NCA.

Results were summarized as:

i. the yearly cumulative[1] number of physicians adopting each NCA over the study period;

ii. the cumulative[1] proportion of physicians adopting each NCA over the study period

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[1] In cumulative analysis, physicians will continue to be counted in cumulative totals in subsequent years after counting even if they have left the NSCLC prescribing pool (i.e. physicians may still be prescribing for other cancers and may re-enter the NSCLC physician prescribing pool).

iii. the yearly non-cumulative proportion of physicians adopting from the pool of physicians who have never prescribed the NCA before (NCA "naïve" physicians).

Time to uptake of a NCA was calculated in three ways:

i. the time from when a physician entered the database (start year) to the adoption year of the NCA.

ii. the time from first evidence favouring usage of the NCA (as determined in chapter 2) to the physician's adoption year of the NCA.

iii. the time from evidence, general recommendations and CCO guidelines (as determined in chapter 2) to the physician's adoption year of the NCA[2].

As data are summarized by year only, baseline years (start year, evidence or recommendation years) were standardized to the start of the year (January). Meanwhile, adoption years were standardized at midway through the respective years (June). For example, time to uptake from start of practice for

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[2] Start year was still used as the baseline reference point for adjusted time to adoption if physician started after the time of evidence, general recommendations or CCO guidelines.

someone starting in the year 2000 and who adopted the same year would be 2000.5 – 2000 = 0.5 years.

3.3. Results

Over the time period 1997-2004, a total of 143 physicians prescribed, at least once, intravenous chemotherapy to advanced lung cancer patients at the 6 regional cancer centers. However, the mean number of physicians actively prescribing per year was 53 (SD 9.4). Only nine physicians prescribed every year throughout the study period. Physicians included medical oncologists, general practitioners in oncology (assistants to medical oncologists) and post-graduate resident trainee physicians. We could not differentiate between different types of physicians. Total number of new prescriptions (new patients treated) of both NCA to patients during this period was 3534.

Vinorelbine

There were a total of 3137 new prescriptions of vinorelbine over the entire period. Yearly new prescriptions (new patients treated) can be seen graphically in Figure 3-1. The number of new prescriptions for vinorelbine initially rose until 2002 then declined in 2003 but this did not appear due to increased prescribing of paclitaxel. Other NCA received CCO funding for first line therapy in NSCLC around that time including gemcitabine (2002) and docetaxel (2003). The cumulative number of physicians adopting each NCA plotted over time can be seen in Figure 3-2. Vinorelbine demonstrates a

linear increase in adoption that parallels the increase in size of the physician population. If we convert the yearly cumulative adopters into a proportion of the yearly cumulative physicians to control for the dynamic changes in population size, we see the resulting curve in Figure 3-3. The curve appears to already be in the plateau phase with a high rate of adoption of ~80%. If we look back to the cohort of nine physicians who prescribed through the study period (Figure 3-5), 100% adopted vinorelbine by 1998.

Overall, most physicians adopted vinorelbine within 1.3 years of entering the database (Table 3-4). Rank order of centres for mean time to adoption revealed centre A (mean 0.56 years) was the earliest adopter by a slim margin over centre E (mean 0.57 years). Centre D was the last to adopt (mean 2.05 years).

Finally, we could not quantify the research-clinical recommendations gap as the CMA (see chapter two) revealed there is insufficient evidence to recommend the use of vinorelbine. Similarly, the study was unable to calculate the clinical recommendations-practice gap for vinorelbine as the mean time from either CCO guidelines or majority of recommendations to physician adoption occurred in 1996, one year before the physician database was able to provide data. Likewise, Health Canada NOC occurred before the physician database. However, we can observe that high rates of adoption existed within 3 years of the guidelines and NOC.

Paclitaxel

There were a total of 397 new prescriptions of paclitaxel over the entire period. Yearly new prescriptions (Figure 3-1) demonstrated a slight early peak until 2002 then a decline. Cumulative number of physicians adopting paclitaxel over time can be seen in Figure 3-2. There was a linear increase in adoption of paclitaxel which does not parallel the increase in size of the physician population, but does rise slowly over time.

When the yearly cumulative number of adopters was converted into a proportion of the yearly cumulative number of physicians to control for the dynamic changes in population size, we see the resulting curve in Figure 3-4. The curve still demonstrated an initial steep rate of uptake. However, paclitaxel appears to reach its plateau in 1998 with less than 50% cumulative level of adoption. It should be noted that during paclitaxel's plateau phase there is a noticeable drop in the proportion of adopters. This likely represents a combination of decreased rate of adoption after 1998, as seen in Table 3-1 and Table 3-2 where the proportion of adopters from the pool of physicians naïve to each NCA is calculated, as well as a cumulative increase in physician population size. If we look back to the cohort of nine physicians who prescribed through the study period (Figure 3-5), 100% adopted paclitaxel by 2001.

Physicians adopted paclitaxel within 2.9 years of the start of practice (Table 3-4), over twice as long as it took physicians to adopt vinorelbine. Rank order of centres for mean time to adoption was the same as for vinorelbine. Centre A was the earliest adopter (mean 2.06 years) by a slim margin over centre E (mean 2.07 years). Again centre D was the last to adopt (mean 4.95 years).

Finally, as with vinorelbine, we could not determine how long it took from the time sufficient positive evidence was published about paclitaxel until a majority of clinical recommendations suggested its use, as the CMA (see chapter 2) revealed there is insufficient evidence to support the use of paclitaxel. The study was also unable to calculate the mean time from release of CCO guidelines to physician adoption as there was never a CCO guideline that made a recommendation on this specific regimen during the study period. However, the study was able to calculate the mean time from when the majority of clinical recommendations supported the use of paclitaxel (general recommendations) (year 2000 as determined in chapter two) to physician adoption (Table 3-5). Mean time to adoption from general recommendations was 1.82 years (SD 2.38 years). On average, no centre adopted prior to release of general recommendations. However, if we look back to the cohort of nine physicians who prescribed through the study period, over half had adopted paclitaxel by 1997 (Figure 3-5) prior to general recommendations (2000), Health Canada NOC (2002), and this despite no CCO guideline recommendation throughout the study period.

3.4. Discussion

Statement of principal findings

This study was successful in its ability to demonstrate the clinical recommendations-practice gap in lung cancer. Using the CCO OPIS database, the study was able to identify the relatively rapid adoption of these two NCA in lung cancer by combining previously reported results (see chapter 2) about the evidence, recommendations and key milestones, with physician prescription data. This study also identified the possibility of premature or inappropriate clinical recommendations-practice gaps.

The study established that vinorelbine had a rapid uptake less than 2 years from start of practice, and high levels of adoption (>80%) throughout the study period. The high levels of adoption occurred within 3 years of Health Canada NOC (first NOC for any site allowing entry into the market), general recommendations, CCO guidelines and CCO funding. Mean time to adoption from start year was also rapid.

This rapid adoption occurred despite the limited amount of evidence and possibly premature or inappropriate recommendations (see chapter 2). Unfortunately, the study was not able to determine if adoption of vinorelbine

occurred prior to or after either CCO recommendations or general recommendations of CPG and textbooks, as these reference points were prior to available physician prescription data.

Meanwhile, paclitaxel also experienced swift uptake, less than 3 years from start of practice, and substantial adoption (~50%) but never became routine practice as the total number of prescriptions was approximately one ninth the number of prescriptions for vinorelbine. This may reflect many factors including: (1) paclitaxel did not receive Health Canada NOC indication for NSCLC until 2002 and was therefore being used "off label" (paclitaxel received Health Canada NOC for ovarian cancer in 1992); (2) the majority of CPG and textbooks only recommended the use of paclitaxel in advanced NSCLC in 2000; (3) there was no CCO guideline supporting its use during the entire study period; and (4) CCO funding did not occur until 2003. Despite CCO funding in 2003, there was not a significant rise in the prescribing rate, which may have reflected competition from other NCA that received CCO funding for first line treatment of NSCLC at the same time (e.g. docetaxel and gemcitabine) (49)

There was less evidence for paclitaxel than vinorelbine to justify recommendations (see chapter 2). Similarly, the research-practice gap may

be premature or inappropriate. No comparison of a gap to CCO guidelines was possible as no guideline, specific to the platinum-paclitaxel combination, had been released by the end of the study period in 2004. So despite no CCO clinical practice guideline, paclitaxel was being used by Ontario physicians.

In contrast to vinorelbine, recommendations by the majority of CPGs and textbooks occurred during the period of available physician prescription data (2000), thus the study was able to demonstrate the clinical recommendations-practice gap with a mean time to adoption in less than 3 years. The study was able to demonstrate that on average the adoption of paclitaxel did not occur prior to general recommendations of CPGs and textbooks.

In attempting to describe the pattern of adoption, various different patterns have been described with the most famous being the S-shaped diffusion curve described by Rogers (Figure 1-3) (13). Both agents were in the late phase of their diffusion with vinorelbine already in the plateau phase and paclitaxel reaching the plateau phase within 2 years of the start of available physician prescription data. Therefore the study was unable to accurately define any pattern of uptake.

Rogers also used his diffusion of innovation theory to classify adopters into different categories from innovators to laggards (13). This study was able to identify early versus late adopters, but is unable to determine which practice was more appropriate (or perhaps neither were appropriate) due to the lack of definitive evidence supporting the use of the drug.

Strengths and weaknesses of the study

The strength of this study was the ability to simultaneously compare evidence, recommendations, key milestones and physician practices over time. This provides the reader with the ability to view the entire spectrum of influences on practice patterns.

In addition, the study's flexibility when defining different reference points (e.g. start year, year of definitive evidence, guideline publication, milestones) granted an ability to quantify the direction and magnitude of different gaps. However, as previously described in chapter two, CMA was unable to provide any definitive evidence supporting either NCA, thereby making it difficult to calculate the research-clinical recommendations gap. Likewise, this lack of definitive evidence did not allow the determination of the direction and magnitude of the research-practice gap. As well, even with a reference starting point for recommendations calculations were limited by a lack of

physician prescription data prior to 1997. Future studies of drugs entering the market after 1997 should not have this problem.

The generalizability of these findings to the entire cancer system may be limited as many patients are seen outside the structured regional cancer system by community oncologist. In addition, the results may not apply to these same NCA in earlier stage disease. The adoption of an innovation can differ significantly based on influences such as local organizational structure (especially funding structure) and exposure to external influences such as opinion leaders.

Strengths and weaknesses in relation to other studies

Previous surveys (11, 12) demonstrated that practice reflected recommendations in only 30-50% of prescribed therapies. Graham et al. surveyed Ontario physicians suggesting that oncologists use recommendations routinely or some of the time approximately 80% of the time (50). This study has been able to quantitatively document that 80% of physicians in the CCO system adopted the recommended therapy with in a relatively short period of time after recommendations. However, the study also demonstrated half of the physicians adopted a therapy (paclitaxel)

without recommendations. Interestingly, paclitaxel was funded by CCO prior to release of clinical recommendations supporting use of the therapy.

Meaning of the study: possible mechanisms and implications for clinicians or policymakers

The study provides us with evidence that physicians in the Ontario cancer system are rapid adopters of novel therapies in advanced NSCLC. It was also able to show there were differences in time to adoption between centres. However, the study was not able to determine the influence of the CCO guideline system on Ontario physicians. The paclitaxel case study allowed comparison of adoption to recommendations; it appeared that adoption followed general recommendations, yet did occur without local guideline recommendations. Therefore if policy makers wish to influence adoption of novel therapies in oncology, timeliness of guideline development may be crucial.

Unanswered questions and future research

Prospective studies are needed to determine the characteristics of the diffusion patterns both inside and outside the formal cancer system. Furthermore, qualitative research to explore the major influences on uptake and regional differences is required. The ultimate goal should be to delineate key elements that lead to minimal and appropriate knowledge translation gaps.

Figures & Tables

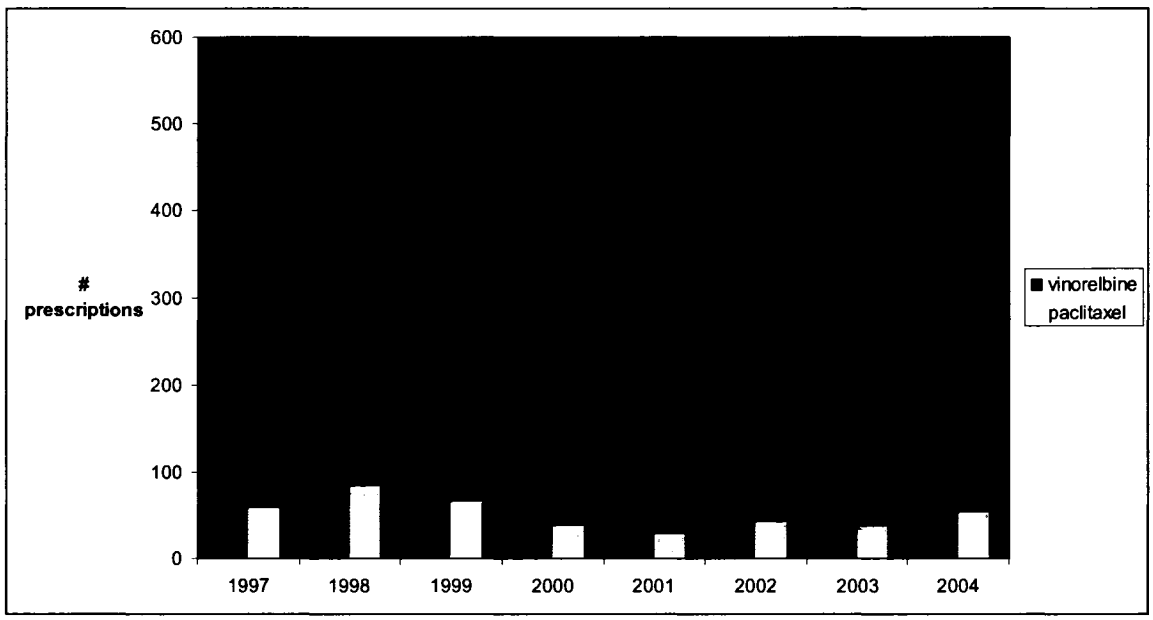


Figure 3-1 Yearly new prescription data

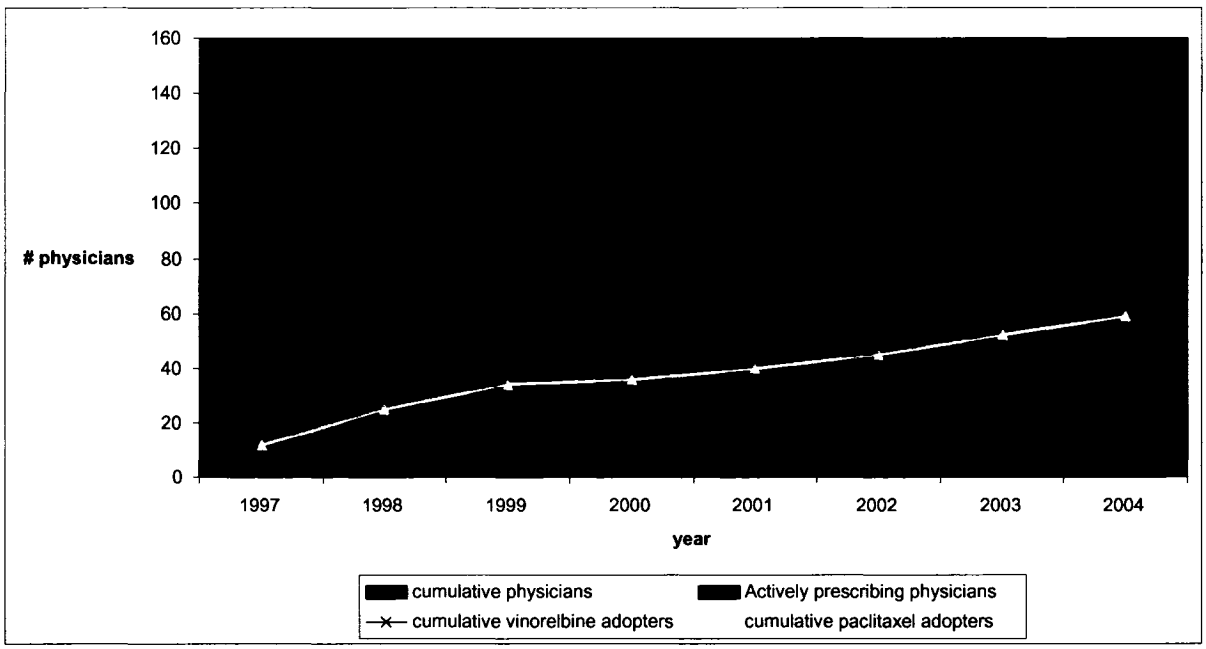
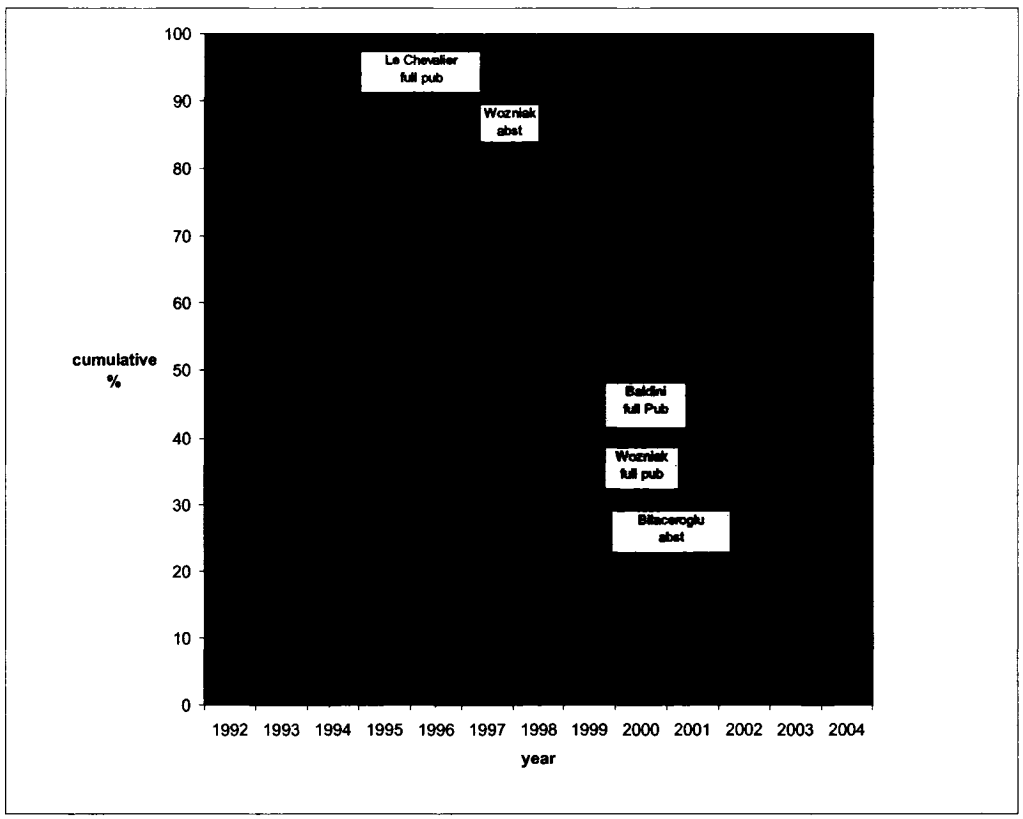


Figure 3-2 Cumulative physician and NCA adopter trends



FDA = US Food and Drug administration,
abst = abstract publication,
full pub = full text publication,
ASCO = American Society of Clinical Oncology,
NSCLC = Non-Small Cell Lung Cancer,
NOC = Health Canada Notice of Compliance,
CCO = Cancer Care Ontario

Figure 3-3 Vinorelbine cumulative proportion diffusion curve (blue line)

with evidence ( ) and key milestone (red boxes) annotations

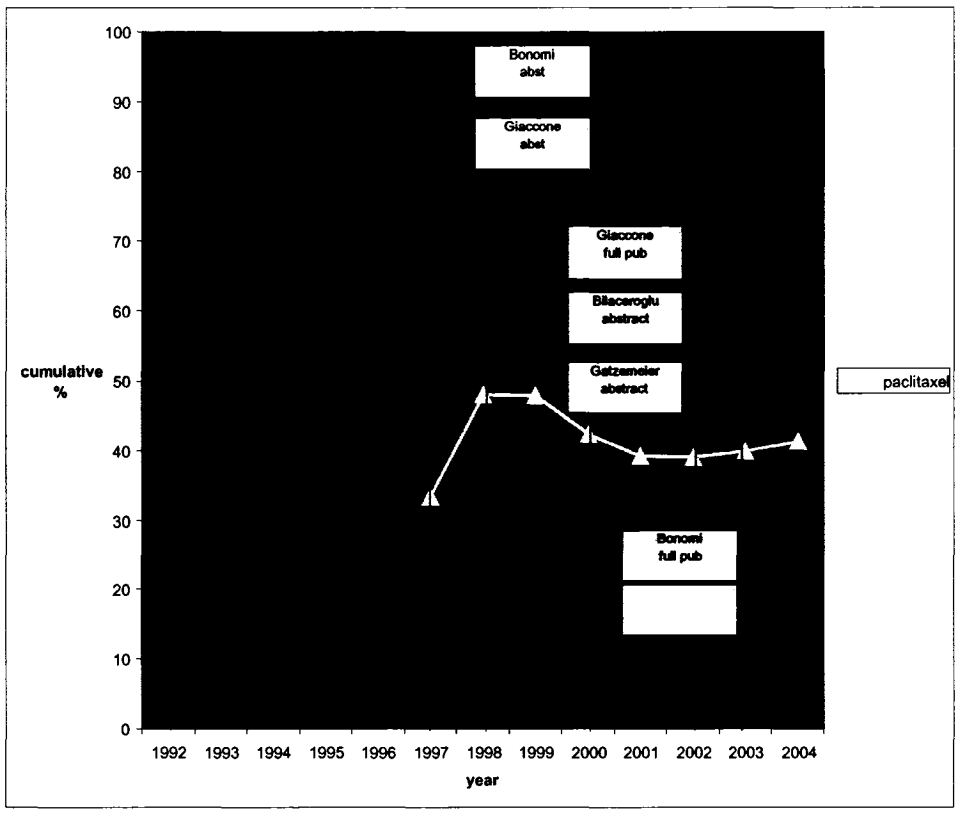


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Figure 3-4 Paclitaxel cumulative proportion diffusion curve ( ) with evidence ( ) and key milestone (red boxes) annotations

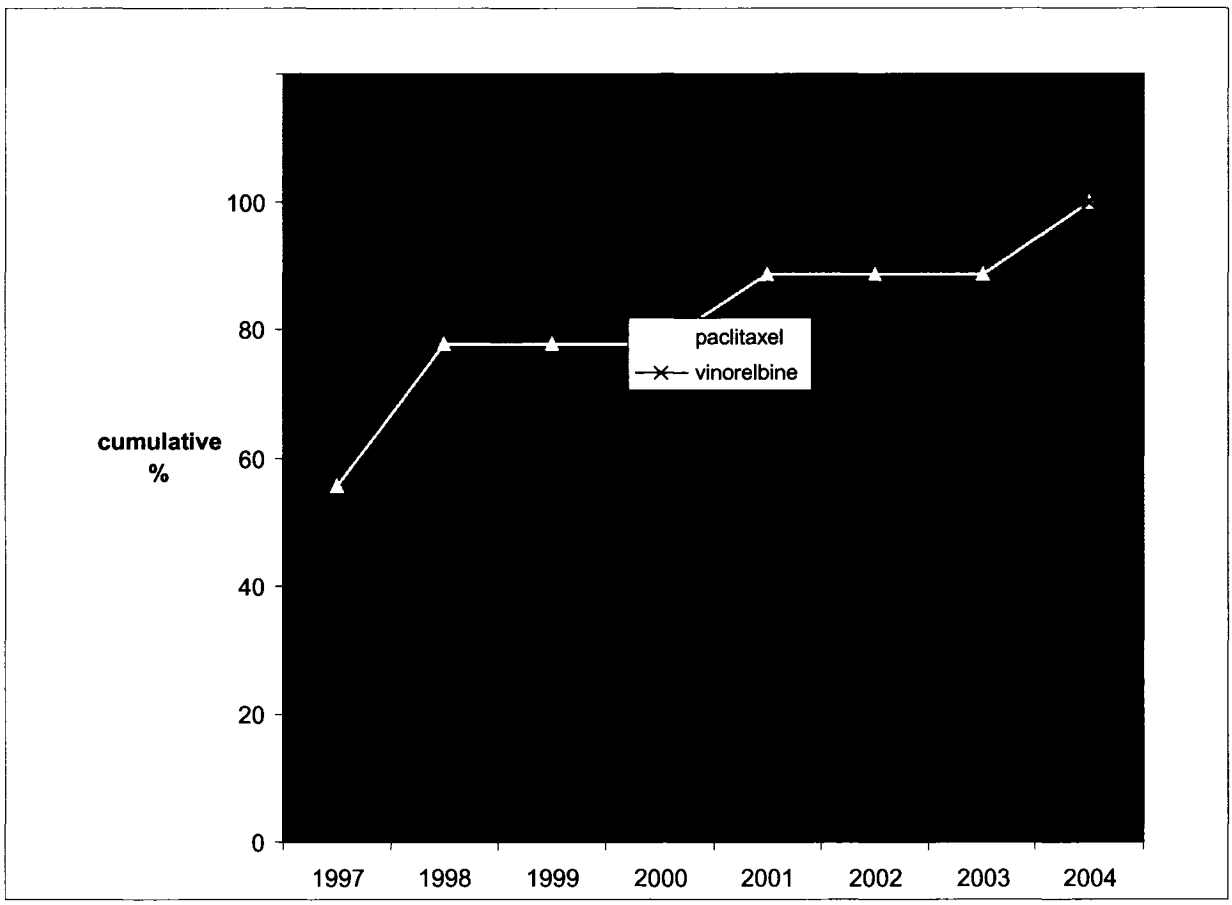

Figure 3-5 Cumulative proportion diffusion curve 1997-2004 physician cohort

Table 3-1 Physician prescribing activity patterns and adoption rates of vinorelbine

	1997	1998	1999	2000	2001	2002	2003	2004
Cumulative # physicians	36	52	71	85	102	115	130	143
# Actively prescribing physicians	36	45	52	53	58	59	65	61
# Vinorelbine naïve physicians	36	18	26	19	18	14	17	16
# Vinorelbine adopting physicians	27	11	16	15	15	13	11	8
naïve physicians adopting vinorelbine	75%	61%	62%	79%	83%	93%	65%	50%

Table 3-2 Physician prescribing activity patterns and adoption rates of paclitaxel

	1997	1998	1999	2000	2001	2002	2003	2004
Cumulative # physicians	36	52	71	85	102	115	130	143
# Actively prescribing physicians	36	45	52	53	58	59	65	61
# paclitaxel naïve physicians	36	35	33	27	35	35	40	36
# paclitaxel adopting physicians	12	13	9	2	4	5	7	7
naïve physicians adopting paclitaxel	33%	37%	27%	7%	11%	14%	18%	19%

Table 3-3 Regional Cancer Centre demographics

	Centre A	Centre B	Centre C	Centre D	Centre E	Centre F
Average # new prescriptions per year	46	211	285	58	66	36
Average # active physicians per year	5.8	13.5	17.9	6.4	5.1	5.0
Cumulative total # physicians 1997-2004	16	42	38	11	14	22
Mean years physician active prescribing	2.88	2.57	3.76	4.64	2.93	1.71

Table 3-4 Regional cancer centre time to uptake (years) from physician start year

		Centre A	Centre B	Centre C	Centre D	Centre E	Centre F	Overall
Vinorelbine	median	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	mean	0.56	1.79	1.00	2.05	0.57	1.31	1.31
	SD	0.25	2.22	1.29	2.73	0.27	2.27	1.85
Paclitaxel	median	2	3.5	1.5	5.5	1.5	2.5	2.5
	mean	2.06	3.48	2.29	4.95	2.07	2.98	2.93
	SD	1.82	2.58	2.12	2.34	1.50	2.42	2.36

Table 3-5 Paclitaxel adjusted time to uptake (years) relative to general recommendations (2000)*

	Centre A	Centre B	Centre C	Centre D	Centre E	Centre F	Overall
Before adjustment							
median	2	3.5	1.5	5.5	1.5	2.5	2.5
mean	2.06	3.48	2.29	4.95	2.07	2.98	2.93
SD	1.82	2.58	2.12	2.34	1.50	2.42	2.36
After adjustment							
median	2	3.5	0.5	4.5	1	2.5	2.5
mean	1.25	2.12	1.05	3.50	1.21	2.45	1.82
SD	2.11	2.80	2.18	1.55	2.05	2.01	2.38

**or physician start date if after recommendation

4. Chapter 4 – Discussion

The goal of this thesis was to perform a pilot study for the Canadian Institutes of Health Research funded project entitled "The Life Cycle of Evidence in Cancer Care". The objective of the project was to investigate the role of evidence in determining clinical recommendations and practice in cancer control. In doing so, the pilot study documented the research-practice gap.

In 1992, Antman and Lau demonstrated a considerable time delay between the publication of randomized controlled trial (RCT) findings and the issuance of clinical recommendations incorporating these findings in the field of cardiology (5, 10). Cancer care was chosen for this project based on the perception that there was more coordination in research (e.g. US National Cancer Institute, National Cancer Institute of Canada, European Organization for Research and Treatment of Cancer) and provision of care (e.g. Cancer Care Ontario (CCO), Canadian Cancer Control Strategy). The research question was intended to explore whether this higher level of coordination would result in better of coordination and quality of research, which would be translated into practice quicker and thus evidence-practice gaps would be shorter.

This pilot study achieved its objective through the case study of two novel chemotherapy agents (NCA) in the treatment of advanced non-small cell lung

cancer (NSCLC). It successfully documented the evidence, clinical recommendations, milestones and level of adoption. It was also innovative by combining these results to provide a complete perspective of the research-practice spectrum. In doing so, it has demonstrated that with respect to these two case studies, research findings about novel therapies (even if studies fail to provide definitive results of effectiveness) are rapidly transferred into clinical recommendations and practice.

The key findings of the study were:

- There is limited evidence for both vinorelbine and paclitaxel to be used as first line therapy in combination with a platinum agent for the treatment of advanced NSCLC;
- Despite the limited evidence, clinical recommendations for the use of these NCA were made resulting in the premature or inappropriate recommendations for the use of these agents;
- Despite limited evidence, both NCA achieved key milestones such as US FDA and Health Canada approval, and CCO funding;
- There were different levels of overall adoption of the two NCA;
- There was rapid adoption of both agents by physicians relative to the time they entered the study;
- There was also rapid adoption of both agents relative to the time the majority of clinical recommendations suggested the use of these NCA;

- Adoption did not necessarily convert practice, as many physicians tried paclitaxel at least once but the volume of prescriptions remained low relative to vinorelbine;
- Adoption by Ontario physicians did not necessarily depend on CCO recommendations or funding; adoption of paclitaxel preceded the publication of CCO clinical practice guidelines and CCO funding, indicating that the CCO clinical recommendations were not in fact guiding practice.

While this pilot study demonstrated the feasibility of the project, it also uncovered many obstacles. This pilot study chose the focused question that considered the incremental effect of the NCA in the most common setting of first line therapy in combination with a platinum agent for advanced NSCLC. It did not look at whether the NCA simply had activity in NSCLC. The systematic review revealed that evidence for this focused question was quite limited.

Another observation was that, relatively early in the evolution of the body of evidence about the effectiveness of an NCA in first line therapy, the NCA soon became part of the control arm in studies. In so doing, this ended the generation of any further studies with the NCA as the experimental arm and any further evolution of the evidence for the NCA's incremental effect. This is another indication of the rapid incorporation of NCA into practice, in this case

the research practice. To demonstrate the relative short NCA evidence generation span, all 10 trials included in this study were published over an eight year period. This is a very short time span compared with Antman and Lau's work that revealed 70 thrombolytic trials were performed over a 30 year period (5, 10).

Many of the published abstracts found in the systematic review are submitted 4-6 months prior to the meetings and results are still being analyzed. Survival results are then presented orally at the meetings and not available to the meta-analyst. This significantly affects the ability for cumulative meta-analysis (CMA) to accurately track the timing of availability of evidence. However, this obstacle may be less of a problem in the future with the advent of the Internet and the ability for people to attend or review posters and presentations "virtually". However this will change the conventional methodology of the systematic review to incorporate more than purely published data.

In addition to the limited availability of data, there was wide variation in reporting of results thereby restricting the methods we could use for the CMA. Only one trial reported a hazard ratio, few included survival curves and some did not give any statistical calculations. However, it should be noted that some of these trials were performed over a decade ago when optimal statistical calculations were more labour intensive. With the advent of current

computing software we may see better reporting of data. Therefore, the study was forced to use the secondary method of CMA, a t-test of survival differences to approximate a random effects model, which may have contributed to the inability of the CMA to provide a statistically significant result.

Similar to limited evidence on this study's focused question, recommendations from clinical practice guidelines and textbooks commonly did not address the focused question and at times discussed the evidence but did not provide any specific recommendation.

Documenting key milestones such as the evidence used to make the recommendations for governmental approval was enlightening. It provided insight into the relative difference in governmental transparency between the US and Canada. The US Federal Drug Administration has embraced the Internet and provided all documentation regarding drug approval online, in well organized and succinct fashion. By contrast, Health Canada provides this data online in a user unfriendly format that is labour intensive to interpret. Personal communication with Health Canada was not able to speed up this process, as documentation methods are not completely automated and depended on institutional memory of key individuals.

While the Ontario Oncology Patient Information System (OPIS) was able to provide physician prescription data, data for the entire period of interest for this study was not available. The study also demonstrated the lack of appropriate information captured by OPIS such as clinical stage and line of treatment. Recent changes in Cancer Care Ontario staging policy (http://www.cancercare.on.ca/documents/StagingPolicy.pdf, April 2005) and the OPIS 2000 interface will address these specific issues.

Study strengths and limitations

One potential criticism of this study is that it focused on survival data alone for determination of benefit. Trials in oncology, in particular for conditions with no cure and relatively few effective treatments, are now resorting to alternative endpoints to represent "clinical benefit" such as response rate, time to progression or quality of life (51). This is a trend seen in the FDA approval process and has been formalized in their accelerated approval process where diseases with poor prognoses and limited treatment options can obtain temporary approval based on alternative endpoints. Nevertheless these endpoints do not guarantee a survival benefit and the FDA still requires phase III evidence prior to full approval.

Despite obstacles, the pilot study was able to demonstrate feasibility of studying the evidence-practice gap using the proposed method. It also demonstrated the evolution of evidence and the relatively greater role a

limited number of early large trials has in influencing oncology recommendations. It has previously been demonstrated that the promising results of early trials do not necessarily withstand the test of time following the publication of subsequent trials (52, 53). In addition, if recommendations depend on only one trial, using traditional levels of significance, this result could be chance alone five percent of the time. Therefore, authors and guideline developers in making recommendations based on early trial results should take great caution.

The implications arising from this pilot study would be:

- Establish guidelines similar to the CONSORT (54) and QUOROM (55) guidelines for consistent and appropriate reporting of survival data; this will allow the results to be better assessed in meta-analytic techniques;
- Encourage researchers to evaluate the evidence from RCTs continuously using such methods as cumulative meta-analysis, to determine the need for further trials and to determine when it is appropriate for the therapy to become the comparator arm.
- Encourage guideline developers to scrutinize the evidence behind clinical recommendations meticulously prior to framing policy and to ensure timely publication and revision of recommendations;
- Prospective studies of adoption of novel therapies should be performed to help identify adoption patterns, uncover factors that

influence appropriate adoption practices and to quantify research-practice gaps.

In conclusion, this pilot study has succeeded in establishing a framework for further studies of existing and future NCA. It has also established a new standard for analyzing the knowledge translation gaps across the entire spectrum from research to practice in oncology.

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APPENDICES

A. TNM staging system

Primary tumour (T)

TX: Primary tumour cannot be assessed, or tumour is proven by the presence of malignant cells in sputum or bronchial washings but is not visualized by imaging or bronchoscopy

T0: No evidence of primary tumour

Tis: Carcinoma in situ

T1: A tumour that is ≤3 cm in greatest dimension, is surrounded by lung or visceral pleura, and is without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus). [*Note: The uncommon superficial tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.*]

T2: A tumour with any of the following features of size or extent:

>3 cm in greatest dimension

Involves the main bronchus and is ≥2 cm distal to the carina

Invades the visceral pleura

Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3: A tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or, tumour in the main bronchus <2 cm distal to the carina but without involvement of the carina; or, associated atelectasis or obstructive pneumonitis of the entire lung

T4: A tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or, separate tumour nodules in the same lobe; or, tumour with a malignant pleural effusion. [*Note: Most pleural effusions associated with lung cancer are due to tumour; however, in a few patients multiple cytopathologic examinations of pleural fluid are negative for tumour. In these cases, fluid is nonbloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element, and the patient should be staged as T1, T2, or T3.*]

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumour

N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis present. [*Note: M1 includes separate tumour nodule(s) in a different lobe (ipsilateral or contralateral).*]

AJCC stage groupings

Occult carcinoma
TX, N0, M0

Stage 0
Tis, N0, M0

Stage I
T1, N0, M0
T2, N0, M0

Stage II
T1, N1, M0
T2, N1, M0
T3, N0, M0

Stage IIIA
T1, N2, M0
T2, N2, M0
T3, N1, M0
T3, N2, M0

Stage IIIB
Any T, N3, M0
T4, any N, M0

Stage IV
Any T, any N, M1

B. Systematic Review Search Strategy

1. exp lung neoplasms/
2. Carcinoma, Non-Small-Cell Lung/
3. NSCLC.tw.
4. (sarcoma$ or adenocarcinom$ or neoplasm$ or cancer$ or tumour$ or tumor$ or carcinoma$ or malignanc$ or squamous or large cell).tw.
5. (Bronch$ or pulmonary or lung$).tw,sh.
6. exp lung/
7. 4 and (5 or 6)
8. 1 or 2 or 3 or 7
9. (metastas$ or metastatic or advanced).tw.
10. exp Neoplasm Metastasis/
11. 9 or 10
12. 8 and 11
13. capecitabine.tw,rn.
14. xeloda.tw.
15. docetaxel.tw,rn.
16. taxotere.tw.
17. exp Doxorubicin/
18. Doxorubicin.rn.
19. (adriamycin or adriablastin or adriablastine or adriblastin or caelyx or dox-sl or doxil or doxorubicin or epirubicin).tw,rn.
20. (fludarabine or fludara).tw.
21. fludarabine.rn.
22. gemcitabine.tw,rn.
23. gemzar.tw.
24. irinotecan.tw,rn.
25. camptosar.tw.
26. Paclitaxel/
27. paclitaxel.tw,rn.
28. (taxol or paxene).tw.
29. raltitrexed.tw,rn.
30. tomudex.tw.
31. Topotecan/
32. Topotecan.tw,rn.
33. (hycamtamine or hycamtin or nsc-609699 or nogitecan hydrochloride or topotecan or sk&f-104864-a or skf-104864-a).tw,rn.
34. vinorelbine.tw,rn.
35. navelbine.tw.
36. or/13-35
37. clinical trial.pt,mp.
38. randomized controlled trial.pt.
39. random$.tw.
40. placebo$.tw.
41. or/37-40
42. 12 and 36
43. 41 and 42
44. limit 43 to human
45. *breast neoplasms/
46. 44 not 45
47. herceptin.tw.
48. temodal.tw.
49. 47 or 48
50. 12 and 49
51. 41 and 50
52. limit 51 to human
53. 44 not 52
54. 44 or 53

C. Systematic Review Data Abstraction Form

C Coding				
C1	Unique code number			
C2	Evaluator			
C3	Date of Extraction			
DD Descriptive Data I				
DD1	First Author			
DD2	Phase			
DD3	Country (leading country if international)			
	International			
SE Study Excluded (reason)				
General Notes 1				
DD Descriptive Data II				
DD7	Multi-center			
	If yes #			
DD8	Source of Funding			
	For profit organization			
	Non-profit organization			
	Other			
	Drug Company Name:			
DD9	Possible conflict of interest			
DD10	Authors affiliated with Drug Company			
DD11	Ontario cancer center participation			
	If yes, name City (Cities)			

TX Treatment				
AA1	How many arms?			
TXA	Cycle week duration arm A			
TXA	# planned cycles for arm A			
TXA	Drug 1A			
	Dose drug 1A			
	# days drug 1A			
	Frequency drug 1A			
TXA	Drug 2A			
	Dose drug 2A			
	# days drug 2A			
	Frequency drug 2A			
TXA	Drug 3A			
	Dose drug 3A			
	# days drug 3A			
	Frequency drug 3A			
TXA	Drug 4A			
	Dose drug 4A			
	# days drug 4A			
	Frequency drug 4A			
TXB	Cycle week duration arm B			
TXB	# planned cycles for arm B			
TXB	Drug 1B			
	Dose drug 1B			
	# days drug 1B			
	Frequency drug 1B			
TXB	Drug 2B			
	Dose drug 2B			
	# days drug 2B			
	Frequency drug 2B			
TXB	Drug 3B			
	Dose drug 3B			
	# days drug 3B			
	Frequency drug 3B			
TXB	Drug 4B			
	Dose drug 4B			
	# days drug 4B			
	Frequency drug 4B			

QA Quality Assessment				
QA1	Generation of allocation sequence			
	Description			
	Adequacy			
QA2	Allocation concealment			
	Description			
	Adequacy			
QA3	Blinding			
	Description			
	Adequacy			
QA4	Losses to follow-up			
	Description			
	Adequacy			
QA5	Intention to treat			
QA6	Sample size calculation			
POP Population				
POP1	Initial time of patient accrual			
POP2	Final time of patient accrual			
POP3	Quality of Life analyses			
	If yes, name scale(s) used:			
	Assessment:			
POP4	Crossover design			
POP5	Line of treatment			
		TXA	TXB	Total
POP6	Number of patients randomised (I)			
POP7	Number of patients analysed			
POP8	Median age			
POP8i	Range age			
POP9	Median follow-up (weeks)			
POP10i	Stage IIIB (#)			
POP10ii	Stage IV (#)			
POP11	Prior chemotherapy (#)			
POP12	Prior adjuvant chemotherapy (#)			
POP13	Prior palliative therapies (#)			
POP14	Prior palliative + adjuvant (#)			
POP15	Brain metasteses			
POP16	Performance status - scale used			
POP17	Performance status 0 / 100 (#)			
POP18	Performance status 1 / 80-90 (#)			
POP19	Performance status 2 / 60-70 (#)			

OC Outcomes				
		TXA	TXB	Total
OC1	Number of patients randomised (II)			
OC1i	Median # cycles			
	Response (#)			
OC2	Patients analysed			
OC3	Complete response			
OC4	Partial response			
OC5	Stable disease			
OC6	Disease progression			
OC7	Overall response (complete + partial)			
OC7i	95% C.I.(lower)			
OC7ii	95% C.I.(upper)			
OC7iii	P value <or =			
OC7iiii	Two sided:			
OC8	Scale used			
	Survival (#)			
OC9	Patients analysed			
OC14	Hazard Ratio - Overall Survival ratio - Intention to treat			
OC14i	95% C.I.(lower)			
OC14ii	95% C.I.(upper)			
OC14iii	P value <or =			
OC14iiii	Two sided:			
OC15	Median Overall Survival (weeks)			
OC15bis1	95% C.I.(lower)			
OC15bis2	95% C.I.(upper)			
OC15bis3	Hazard Ratio - Overall Survival ratio - By protocol			
OC15i	95% C.I.(lower)			
OC15ii	95% C.I.(upper)			
OC15iii	P value <or =			
OC15iiii	Two sided:			
OC16	Patients died at the end of the study (#)			
	Progression Free Survival (PFS) (#)			
OC17	Patients analysed			
OC22	Hazard Ratio - Overall progression ratio - Intention to treat			
OC22i	95% C.I.(lower)			
OC22ii	95% C.I.(upper)			
OC22iii	P value:			

OC22iiii	Two sided:			
OC23	Median Overall progression (weeks)			
OC23bis1	95% C.I.(lower)			
OC23bis2	95% C.I.(upper)			
OC23bis3	Hazard ratio - Overall progression ratio - By protocol			
OC23i	95% C.I.(lower)			
OC23ii	95% C.I.(upper)			
OC23iii	P value <or =			
OC23iiii	Two sided:			
OC24	Patients progressed at the end of the study (#)			
Notes	Item #			
Notes	Item #			
OC25	Blinded assessors for imaging tests			
SD Side Effects (# of patients with WHO grade 3/4)				
	Nonhaematologic	TXA	TXB	Total
SD1	Patients analysed			
SD2	Alopecia			
SD3	Asthenia (fatigue)			
SD4	Cardiovascular toxicity			
SD5	Constipation			
SD6	Diarrhoea			
SD7	Fever (pyrexia)			
SD8	Fluid retention			
SD9	Infection			
SD10	Nausea			
SD11	Nephrotoxicity			
SD12	Neurosensory disorders			
SD13	Pain			
SD14	Pulmonary toxicity			
SD15	Skin toxicity			
SD16	Stomatitis			
SD17	Vomiting			
TOXD	Death related to treatment			
DISD	Discontinuity related to toxicity			
	Haematologic	TXA	TXB	
SD1_haematol	Patients analysed			
SD18	Anaemia			

SD19	Febrile neutropenia			
SD20	Leukopenia			
SD21	Neutropenia			
SD22	Thrombocytopenia			
	Conclusions in trial			
CT1	Scale Used to Grade Conclusions in Trials - Abstract			
CT2	Scale Used to Grade Conclusions in Trials - Full text			

D. Systematic Review: Vinorelbine included references

Trial	Reference author	Year	Title	Abs/Pub	Journal
Le Chevalier	Le Chevalier T	1992	A European multicentre randomized study comparing navelbine alone vs navelbine-cisplatin vs vindesine-cisplatin in 612 patients with advanced non small cell lung cancer	abs	ASCO proceedings
Le Chevalier	Le Chevalier T	1994	Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients.[see comment]	pub	Journal of Clinical Oncology
Le Chevalier	Le Chevalier T	1994	A three-arm trial of vinorelbine (Navelbine) plus cisplatin, vindesine plus cisplatin, and single-agent vinorelbine in the treatment of non-small cell lung cancer: an expanded analysis	pub	Seminars in Oncology
Baldini	Baldini E	1995	Cisplatin, vindesine, mitomycin (MVP) vs cisplatin, ifosamide, navelbine (PIN) vs carboplatin, navelbine (CAN) in advanced non-small cell lung cancer (NSCLC)	abs	European Journal of Cancer
Baldini	Pennucci MC	1995	Cisplatin, vindesine, mitomycin (MVP) vs cisplatin, ifosfamide, navelbine (PIN) vs carboplatin, navelbine (CaN) for stage IIIB/IV non-small cell lung cancer (NSCLC) patients (pts): a randomized phase II FONICAP trial (Meeting abstract)	abs	ASCO proceedings
Le Chevalier	Le Chevalier T	1996	[Results of a randomized study comparing combination of navelbine-cisplatin to combination of vindesine-cisplatin and to navelbine alone in 612 patients with inoperable non-small cell lung cancer]. [French]	pub	Bulletin du Cancer
Wozniak	Wozniak AJ	1996	Randomized phase III trial of cisplatin (CDDP) vs CDDP plus navelbine (NVB) in treatment of advanced non-small cell lung cancer (NSCLC): report of a Southwest Oncology Group study (SWOG-9308) (Meeting abstract)	abs	ASCO proceedings
Le Chevalier	Le Chevalier T	1997	Six year follow up of the european multicentre randomised study comparing navelbine (NVB) alone vs NVB + cisplatin (CDDP) vs vindesine (VDS) + CDDP in 612 patients (PTS) with advanced non-small cell lung cancer (NSCLC)	abs	Thorax
Le Chevalier	Le Chevalier T	1997	Six year follow up of the European Multicentre Randomised Study comparing Navelbine (NVB) alone vs NVB + cisplatin (CDDP) vs vindesine (VDS) + CDDP in 612 patients (pts) with advanced non-small cell lung cancer (NSCLC)	abs	Lung Cancer
Gebbia	Gebbia V	1997	Randomized phase III trial of mitomycin plus vindesine and cisplatin versus vinorelbine and cisplatin in stage III-IV non-small cell lung cancer: a Southern Italy Oncology Group study (G.O.I.M.)	abs	Lung Cancer

Baldini	Baldini E	1998	Cisplatin-vindesine-mitomycin (MVP) vs cisplatin-ifosfamide-vinorelbine (PIN) vs carboplatin-vinorelbine (CaN) in patients with advanced non-small-cell lung cancer (NSCLC): a FONICAP randomized phase II study. Italian Lung Cancer Task Force (FONICAP)	pub	British Journal of Cancer
Wozniak	Wozniak AJ	1998	Randomized phase III trial of cisplatin (CDDP) vs. CDDP plus navelbine (NVB) in treatment of advanced non-small cell lung cancer (NSCLC): an update of a Southwest Oncology Group Study (SWOG-9308) (Meeting abstract)	abs	ASCO proceedings
Wozniak	Wozniak AJ	1998	Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study.[see comment]	pub	Journal of Clinical Oncology
Bilaceroglu	Bilaceroglu S K	1998	Cisplatin/etoposide versus cisplatin/vinorelbine versus cisplatin/paclitaxel in advanced non-small cell lung cancer: a phase III randomized trial [abstract]	abs	European Respiratory Journal -
Gebbia	Gebbia V	1998	Mitomycin C plus vindesine and cisplatin (MVP) versus vinorelbine and cisplatin (PV) in Stage III-IV non small cell lung cancer: a randomized phase III trial of the Southern Italy Oncology Groups Study (GOIM) (Meeting abstract)	abs	ASCO proceedings
Le Chevalier	Soria JC	1999	Prognostic analysis of survival in the European randomized trial comparing navelbine (NVB) vs navelbine cisplatin (NVB-P) vs vindesine cisplatin (NVB-P) (Meeting abstract)	abs	ASCO proceedings
Melo	Costa A	2000	Preliminary results of a randomised phase III trial comparing four cisplatin (P)-based regimens in the treatment of locally advanced and metastatic non-small cell lung cancer (NSCLC)	abs	Lung Cancer
Gebbia	Galetta D	2000	A randomized phase III trial of the Southern Italy Oncology Group (G.O.I.M.) of mitomycin C plus vindesine and cisplatin (MVP regimen) versus vinorelbine plus cisplatin (PV regimen) in stage III-IV non small cell lung cancer	abs	Lung Cancer
Le Chevalier	Le Chevalier T	2001	Long term analysis of survival in the European randomized trial comparing vinorelbine/cisplatin to vindesine/cisplatin and vinorelbine alone in advanced non-small cell lung cancer	pub	Oncologist
Melo	Melo MJ	2002	Results of a randomized phase III trial comparing 4 cisplatin (P)-based regimens in the treatment of locally advanced and metastatic non-small cell lung cancer (NSCLC): mitomycin/vinblastine/cisplatin (MVP) is no longer a therapeutic option	abs	ASCO proceedings
Gebbia	Gebbia V	2002	Vinorelbine plus cisplatin versus cisplatin plus vindesine and mitomycin C in stage IIIB-IV non-small cell lung carcinoma: a prospective randomized study	pub	Lung Cancer

E. Systematic Review: Paclitaxel included references

Trial	Reference Author	Year	Title	Abs/Pub	Journal
Bonomi	Johnson DH	1995	Phase III trial (E5592) comparing cisplatin plus etoposide with cisplatin plus paclitaxel at two dose levels for treatment of advanced non-small-cell lung cancer. Eastern Cooperative Oncology Group	pub	Journal of the National Cancer Institute Monographs
Giaccone	Giaccone G	1995	Teniposide-cisplatin vs paclitaxel-cisplatin in advanced non-small cell lung cancer (NSCLC). Results of a randomized phase II study of the EORTC-LCCG (Meeting abstract)	abs	ASCO proceedings
Giaccone	Giaccone G	1996	Paclitaxel-cisplatin versus teniposide-cisplatin in advanced non-small cell lung cancer (NSCLC) (Meeting abstract)	abs	ASCO proceedings
Giaccone	Scagliotti G	1996	Teniposide/cisplatin versus paclitaxel/cisplatin in advanced non-small cell lung cancer: interim results of a randomized phase III study of the EORTC Lung Cancer Cooperative Group. European Organization for Research and Treatment of Cancer, Lung Cancer Cooperative Group [abstract]	abs	European Respiratory Journal -
Bonomi	Bonomi P	1997	Cisplatin/etoposide vs paclitaxel/cisplatin/G-CSF vs paclitaxel/cisplatin in non-small-cell lung cancer	pub	Oncology (Huntington)
Bonomi	Bonomi P	1997	Comparison of survival for stage IIIB vs stage IV non-small call lung cancer (NSCLC) patients treated with etoposide-cisplatin vs Taxol-cisplatin: an Eastern Cooperative Group trial	abs	ASCO proceedings
Giaccone	Giaccone G	1997	Final results of an EORTC phase III study of paclitaxel vs teniposide, in combination with cisplatin, in advanced NSCLC (Meeting abstract)	abs	ASCO proceedings
Giaccone	Giaccone G	1997	Cisplatin/paclitaxel vs cisplatin/teniposide for advanced non-small-cell lung cancer. The EORTC Lung Cancer Cooperative Group. The European Organization for Research and Treatment of Cancer	pub	Oncology (Huntington)
Giaccone	Giaccone G	1998	Randomized study of paclitaxel-cisplatin versus cisplatin-teniposide in patients with advanced non-small-cell lung cancer. The European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group.[see comment]	pub	Journal of Clinical Oncology
Bilaceroglu	Bilaceroglu S K	1998	Cisplatin/etoposide versus cisplatin/vinorelbine versus cisplatin/paclitaxel in advanced non-small cell lung cancer: a phase III randomized trial [abstract]	abs	European Respiratory Journal
Gatzemeier	Gatzemeier U	1998	Phase III comparative study of high-dose cisplatin (HD-CIS) versus a combination of paclitaxel (TAX) and cisplatin (CIS) in patients with advanced non-small cell lung cancer (NSCLC) (Meeting abstract)	abs	ASCO proceedings
Gatzemeier	Gatzemeier U	1998	Cisplatin vs. Paclitaxel/Cisplatin in advanced non-small cell lung cancer: A phase 3 study	abs	Journal of Cancer Research & Clinical Oncology
Bonomi	Rowinsky EK	1999	Paclitaxel steady-state plasma concentration as a determinant of disease outcome and toxicity in lung cancer patients treated with paclitaxel and cisplatin	pub	Clinical Cancer Research
Bonomi	Bonomi P	2000	Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial	pub	Journal of Clinical Oncology
Gatzemeier	Gatzemeier U	2000	Phase III comparative study of high-dose cisplatin versus a combination of paclitaxel and cisplatin in patients with advanced non-small-cell lung cancer.[see comment]	pub	Journal of Clinical Oncology
Bonomi	Langer CJ	2002	Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial.[see comment]	pub	Journal of the National Cancer Institute

F. Vinorelbine Cumulative Meta-analysis: R programming code

```
#data
Code <- c("Lung009", "Lung007", "Lung202", "Lung185", "Lung030",
"Lung031", "Lung034", "Lung243", "Lung113")

Trial <- c("Le Chevalier", "Le Chevalier", "Wozniak", "Wozniak", "Wozniak",
"Baldini", "Bilaceroglu", "Costa", "Gebbia I")

Year <- c(1994, 1994, 1996, 1998, 1998, 1998,  1998, 2002, 2002)

Month <- c(0.0833333333333333, 0.75, 0.333333333333333,
0.333333333333333, 0.5, 0.55, 0.666666666666667,  0.333333333333333,
0.583333333333333)

Status <- c("s", "s", "a", "a", "s", "s", "a", "a", "s")

survival_median_txa <- c(40, 40, 28, 32, 32, 31.6, 36.5, 36, 28)

survival_median_txb = c(32, 32, 24, 24, 24, 33.6, 33.5, 25.6, 32)
medsurv<-
data.frame(Code,Trial,Year,Month,Status,survival_median_txa,survival_medi
an_txb)
medsurv$Trial <-as.character(medsurv$Trial)


#make numeric date of publication
dates<--(medsurv$Year + medsurv$Month)

#calc differ in median survival
realdata<-medsurv$survival_median_txa - medsurv$survival_median_txb

#get part of study name
nn<-substr(medsurv$Trial,1,5)

#get status of publication
ss<-medsurv$Status

#put data together
xx<-
data.frame(dates=dates,diff=realdata,label=paste(ss,as.numeric(factor(medsu
rv$Tria)),sep=""),printl=paste(nn,"-",ss,sep=""))
xx$id<-paste(xx[,3],dates)

#look at first entry
xx[1,]
```

```
#function to do t.test method on differences in median survival
marefoo<-function(ll){
(c(t.test(ll)$estimate,t.test(ll)$conf))
}

#plot the first few entries before a pooling is possible
plot(c(-16,16),c(-1990,-2005),type="n",xlab="Diff in Median Weeks of
Survival",ylab="Year of Publication")
for(i in 1:2){
text(xx[i,2],xx[i,1],substr(as.character(xx[i,3]),1,1))
text(-14,xx[i,1],as.character(xx[i,4]))
}

#plot the rest of entries where pooling is possible
for(i in 3:length(xx[,1])){

#take all studies before
xs<-xx[1:i,]
ss<-split(xs[,c("id","diff")], substr(as.character(xs[,3]),2,2))

#function to use most recent published result
foomr<-function(x){
x[order(as.numeric(substring(x[,1],3)) + 10000*is.na(x[,2])),1][1]
}

#get most recent results for all studies up to this date
xs<-xs[match(sapply(ss,foomr),xs$id),]
xs<-xs[order(-xs$dates),]
#if it can be pooled by t.test do that otherwise return missing values
if(var(xs[,2],na.rm=T) > 0) cma<-marefoo(xs[,2])
else cma<-rep(NA,3)
print(xs)
print(cma)
#for most recent results plot pooled result at time "j"
j<-nrow(xs)
text(xs[j,2],xs[j,1],substr(as.character(xs[j,3]),1,1))
text(cma[1],xs[j,1],"P")
text(cma[2],xs[j,1],"|")
text(cma[3],xs[j,1],"|")
lines(c(cma[2],cma[3]),c(xs[j,1],xs[j,1]))
text(-14,xs[j,1],as.character(xs[j,4]))}
abline(v=0)
```

G. Paclitaxel Cumulative Meta-analysis: R programming code

```
#data
Code<-
c("Lungxyz","Lung197","Lung032","Lung033","Lung186","Lung058","Lung034"
,"Lung072")
Trial<-
c("Bonomi","Giaccone","Giaccone","Gatzemeier","Gatzemeier","Gatzemeier","
Bilaceroglu","Bonomi")
Year <-c(1997,1997,1998,1998,1998,1998,1998,2000)
Month <- c(0.4,0.3333333,0.4166666,0, 0.3333333,0.75,0.80, 0)
Status <- c("a","a","s","a","a","s","a","s")
survival_median_txa <- c(39,41,42,35,35,35,40,44)
survival_median_txb <- c(31,42,43,37,37,37,33.5,33)
medsurv<-
data.frame(Code,Trial,Year,Month,Status,survival_median_txa,survival_medi
an_txb)
medsurv$Trial <-as.character(medsurv$Trial)
#make numeric date of publication
dates<-(medsurv$Year + medsurv$Month)
#calc differ in median survival
realdata<-medsurv$survival_median_txa - medsurv$survival_median_txb
#get part of study name
nn<-substr(medsurv$Trial,1,5)
#get status of publication
ss<-medsurv$Status
#put data together
xx<-
data.frame(dates=dates,diff=realdata,label=paste(ss,as.numeric(factor(medsu
rv$Trial)),sep=""),printl=paste(nn,"-",ss,sep=""))
xx$id<-paste(xx[,3],dates)
#look at first entry
xx[1,]
#function to do t.test method on differences in median survival
marefoo<-function(ll){
(c(t.test(ll)$estimate,t.test(ll)$conf))
}
xx<-xx[order(xx$dates),]
xx$dates<--xx$dates
#plot the first few entries before a pooling is possible
plot(c(-16,16),c(-1997,-2003),type="n",xlab="Diff in Median Weeks of
Survival",ylab="Year of Publication")
for(i in 1:1){
text(xx[i,2],xx[i,1],substr(as.character(xx[i,3]),1,1))
text(-14,xx[i,1],as.character(xx[i,4]))
}
```

```
#plot the rest of entries where pooling is possible
for(i in 2:length(xx[,1])){
#take all studies before
xs<-xx[1:i,]
ss<-split(xs[,c("id","diff")], substr(as.character(xs[,3]),2,3))
#function to use most recent published result
foomr<-function(x){
x[order(-(as.numeric(substring(x[,1],3)) + 10000*is.na(x[,2]))),1][1]
}
#get most recent results for all studies up to this date
xs<-xs[match(sapply(ss,foomr),xs$id),]
xs<-xs[order(-xs$dates),]
#if it can be pooled by t.test do that otherwise return missing values
if(var(xs[,2],na.rm=T) > 0) cma<-marefoo(xs[,2])
else cma<-rep(NA,3)
print(xs)
print(cma)
#for most recent results plot pooled result at time "j"
j<-nrow(xs)
text(xs[j,2],xs[j,1],substr(as.character(xs[j,3]),1,1))
text(cma[1],xs[j,1],"P")
text(cma[2],xs[j,1],"|")
text(cma[3],xs[j,1],"|")
lines(c(cma[2],cma[3]),c(xs[j,1],xs[j,1]))
text(-14,xs[j,1],as.character(xs[j,4]))
}
abline(v=0)
```

H. Vinorelbine Cumulative Meta-analysis: R program data output

```
     dates      diff  label  printl          id
2 -1994.750   8   s5     Le Ch-s        s5 -1994.75
3 -1996.333   4   a6     Wozni-a        a6 -1996.33333333333
summary value  6.00000 CI (-19.41241  31.41241)                ← 1996 result

    dates      diff  label  printl          id
2 -1994.750   8   s5     Le Ch-s        s5 -1994.75
4 -1998.333   8   a6     Wozni-a        a6 -1998.33333333333
[1] NA NA NA (no change in data)

    dates     diff    label  printl          id
2 -1994.75   8      s5     Le Ch-s        s5 -1994.75
5 -1998.50   8      s6     Wozni-s        s6 -1998.5
[1] NA NA NA  (no change in data)

    dates     diff    label  printl          id
2 -1994.75   8      s5     Le Ch-s        s5 -1994.75
5 -1998.50   8      s6     Wozni-s        s6 -1998.5
6 -1998.55   -2     s1     Baldi-s        s1 -1998.55
summary value  4.666667 CI (-9.675509 19.008842)

    dates     diff    label  printl          id
2 -1994.750   8      s5     Le Ch-s        s5 -1994.75
5 -1998.500   8      s6     Wozni-s        s6 -1998.5
6 -1998.550   -2     s1     Baldi-s        s1 -1998.55
7 -1998.667   3      a2     Bilac-a        a2 -1998.66666666667
summary value 4.250000 CI (-3.367401 11.867401)                ← 1998 final result

    dates     diff    label  printl          id
2 -1994.750  8.0    s5     Le Ch-s        s5 -1994.75
5 -1998.500  8.0    s6     Wozni-s        s6 -1998.5
6 -1998.550 -2.0    s1     Baldi-s        s1 -1998.55
7 -1998.667  3.0    a2     Bilac-a        a2 -1998.66666666667
8 -2002.333 10.4    a3     Costa-a        a3 -2002.33333333333
summary value 5.48000  CI (-0.69745  11.65745)

    dates     diff    label  printl          id
2 -1994.750  8.0    s5     Le Ch-s        s5 -1994.75
5 -1998.500  8.0    s6     Wozni-s        s6 -1998.5
6 -1998.550 -2.0    s1     Baldi-s        s1 -1998.55
7 -1998.667  3.0    a2     Bilac-a        a2 -1998.66666666667
8 -2002.333 10.4    a3     Costa-a        a3 -2002.33333333333
9 -2002.583 -4.0    s4     Gebbi-s        s4 -2002.58333333333
summary value 3.900000 CI (-2.289002 10.089002)                ← 2002 final result
```

dates = date of publication

diff = difference in median survival between study arms in weeks

I. Paclitaxel Cumulative Meta-analysis: R program data output

```
     dates    diff  label  printl          id
2 -1997.333  -1    a4    Giacc-a       a4 1997.3333333
1 -1997.400   8    a2    Bonom-a       a2 1997.4
summary value  3.50000 CI (-53.67792  60.67792)          ← 1997 result

     dates    diff  label  printl          id
2 -1997.333  -1    a4    Giacc-a       a4 1997.3333333
1 -1997.400   8    a2    Bonom-a       a2 1997.4
4 -1998.000  -2    a3    Gatze-a       a3 1998
 summary value 1.666667CI (-12.014897  15.348230)

     dates    diff  label  printl          id
2 -1997.333  -1    a4    Giacc-a       a4 1997.3333333
1 -1997.400   8    a2    Bonom-a       a2 1997.4
5 -1998.333  -2    a3    Gatze-a       a3 1998.3333333
summary value 1.666667 CI (-12.014897  15.348230)

     dates    diff  label  printl          id
1 -1997.400   8    a2    Bonom-a       a2 1997.4
5 -1998.333  -2    a3    Gatze-a       a3 1998.3333333
3 -1998.417  -1    s4    Giacc-s       s4 1998.4166666
 summary value 1.666667 CI (-12.014897  15.348230)

     dates    diff  label  printl          id
1 -1997.400   8    a2    Bonom-a       a2 1997.4
3 -1998.417  -1    s4    Giacc-s       s4 1998.4166666
6 -1998.750  -2    s3    Gatze-s       s3 1998.75
 summary value 1.666667 CI (-12.014897  15.348230)

     dates    diff  label  printl          id
1 -1997.400  8.0   a2    Bonom-a       a2 1997.4
3 -1998.417 -1.0   s4    Giacc-s       s4 1998.4166666
6 -1998.750 -2.0   s3    Gatze-s       s3 1998.75
7 -1998.800  6.5   a1    Bilac-a       a1 1998.8
summary value 2.875000 CI (-5.248424 10.998424)        ← 1998 final result

     dates    diff  label  printl          id
3 -1998.417 -1.0   s4    Giacc-s       s4 1998.4166666
6 -1998.750 -2.0   s3    Gatze-s       s3 1998.75
7 -1998.800  6.5   a1    Bilac-a       a1 1998.8
8 -2000.000 11.0   s2    Bonom-s       s2 2000
summary value  3.625000 CI (-6.256291 13.506291)       ← 2000 final result
```

dates = date of publication

diff = difference in median survival between study arms in weeks

J. Review of recommendations: Clinical Practice Guidelines reviewed

GUIDELINE DEVELOPER	YEAR	TITLE
American College of Chest Physicians	2003	Chemotherapeutic management of stage IV non-small cell lung cancer.
ASCO	1997	Clinical Practice Guidelines on the Treatment of Unresectable Non-Small Cell Lung Carcinoma
	2003	ASCO Treatment of Unresectable Non-Small Cell Lung Carcinoma
National Cancer Institute (PDQ)	1992004	Non-Small Cell Lung Cancer: Treatment
National Comprehensive Cancer Network	1996	NCCN Practice Guidelines for Non-Small-Cell Lung Cancer
	2000	NCCN Practice Guidelines for Non-Small-Cell Lung Cancer
	2001	NCCN Practice Guidelines for Non-Small-Cell Lung Cancer
	2002	NCCN Practice Guidelines in Oncology: Non-Small Cell Lung Cancer
	2003	NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer
	2004	NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer
National Health and Medical Research Council - Australia	2003	Clinical Practice Guidelines for the Management of Lung Cancer - DRAFT
	2004	Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer
NICE	2001	Guidence on the use of docetaxel, paclitaxel, gemcitabine and vinorelbine for the treatment of non-small cell lung carcinoma
PGI: CCO and Ontario Ministry of Health and Long Term Care	1996	Chemotherapy in stage IV (metastatic) non-small cell lung cancer.
	2002	Chemotherapy in stage IV (metastatic) non-small cell lung cancer.
PGI: CCO and Ontario Ministry of Health and Long Term Care	1996	Use of vinorelbine in non-small cell lung cancer.
	2001	Use of vinorelbine in non-small cell lung cancer.
Scottish Intercollegiate Guidelines Network	1998	Management of Lung Cancer
	2005	Management of patients with lung cancer

K. Review of recommendations: textbook sources

Abeloff, M.	*Clinical Oncology*	1st		1995
		2nd*		2000
Bertino, Joseph R., et al, eds	*Encyclopedia of Cancer*	1st*		1997
		2nd		2002
DeVita, Vincent T., et al, eds	*Biologic Therapy of Cancer*			1995
	Cancer: Principles & Practice	4th		1993
		5th		1997
		6th		2001
Haskell, Charles, M.	*Cancer Treatment*	4th		1995
		5th		2001
Holland, James, et. Al eds	*Cancer Medicine*	3rd		1993
		4th		1997
Blast and Holland	*Cancer Medicine*	5th		2000
		6th		2003
Calabresi and Schein	*Medical Oncology*	2nd		1993
Pass, Harvey I, James B Mitchell, and David Johnson	*Lung Cancer Principles and Practice*	1st		1996
		2nd		2000
Joseph Aisner, Rodrigo Arriagada, Mark Green et al	*Comprehensive Textbook of Thoracic Oncology*			1996
Jack Roth, John Ruckdeschel, Thomas Weisenburger et al	*Thoracic Oncology*		2nd	1995

*unable to obtain copies for review

L. Guideline manual electronic search

RESOURCE	LOCATION
National Guidelines Clearing House (NGC)	www.guideline.gov
Guidelines International Network (GIN)	www.g-i-n.net
Cancer Care Ontario (CCO)	www.cancercare.on.ca
Agency for Healthcare Research and Quality (AHRQ)	www.ahrq.gov
National Institute for Clinical Excellence (NICE, UK)	www.nice.org.uk
Evidence Based Medicine Resource Center	www.ebmny.org
American Society of Clinical Oncology (ASCO)	www.asco.org
Canadian Clinical Practice Guidelines (Infobase)	www.cma.ca
Queen's university CPG	http://post.queensu.ca/~bhc/gim/cpgs.html