A Model to Select Regimens for Phase III Trials for Patients with Advanced-Stage Non-Small Cell Lung Cancer

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Abstract

**Purpose:** Historical data from pilot, Phase II, and Phase III studies for patients with advanced-stage non-small cell lung cancer (NSCLC) were used to evaluate a statistical model developed to provide assistance in selecting regimens from pilot studies for subsequent use in larger Phase III randomized studies.

**Experimental Design:** Information from 33 Phase III trials for patients with advanced-stage NSCLC performed from 1973 and 1994 in the United States and Canada was collected. The data from antecedent pilot or Phase II and subsequent Phase III trials were analyzed using a predictive statistical model. This model uses the number of patients in the pilot/Phase II study, the median survival of patients in the pilot, and the number of deaths observed, to estimate the statistical likelihood that the pilot regimen will be shown superior to standard therapy in a subsequent Phase III trial.

**Results:** Ten pilot/Phase II studies were identified that preceded eleven subsequent Phase III studies. The three pilot regimens associated with Phase III trials, revealing statistically significant longer survival, had an expected power of 0.69, 0.85, and 0.94 respectively. The regimens from the seven other pilot studies for which the median power expected was 0.38 (range, 0.07–0.80) showed no difference when compared with standard treatment in a Phase III trial.

**Conclusion:** The use of the expected power model provides an important enhancement to the screening of new therapies. Regimens with an expected power of >0.55 may be good candidates for testing in Phase III trials.

Introduction

Phase III randomized trials for patients with advanced-stage NSCLC performed in the United States and Canada between 1973 and 1994 were recently evaluated to determine the trend in characteristics of these trials (1). Unfortunately, only 5 of the 33 trials Phase III randomized trials (15%) showed a statistically significantly longer survival in the experimental arm, and the survival differences in these studies were quite modest: 0.7–2.7 months. These results show that, in the majority of cases, the experimental regimen did not result in longer survival in a randomized study despite the optimism of investigators after the results of a pilot or Phase II trial were known.

Similiar issues were reported in an analysis of patients with extensive-stage small cell lung cancer (2).

Phase III randomized clinical trials are the accepted method for determining whether a particular therapeutic regimen prolongs the survival duration of patients compared with existing standard regimens. Phase III trials involve large numbers of patients, are expensive, and time consuming. Most Phase III trials are justified based on an informal review of response rates and survival for the same experimental regimen. However, the results of the evaluations of Phase III trials in either patients with extensive-stage small cell lung cancer or advanced-stage NSCLC show that clinical investigators frequently select inappropriate regimens to bring forth to Phase III evaluation (1, 2).

We believe that data from pilot/Phase II trials can be better used to help decide which regimens should be brought forward to Phase III trial. A statistical model proposed from the retrospective study of patients with extensive small cell lung cancer designed with similar intent is now being evaluated prospectively within the cooperative group setting (3). While we await the results of the potential success of this former model in a prospective analysis, we believed it was important to adapt the model to the retrospective data available from the therapeutic trials for patients with advanced NSCLC. NSCLC is more frequent than small cell lung cancer, and the patient benefit of chemotherapy is more controversial compared with the benefit to patients with small cell lung cancer.

The predictive model for patients with advanced-stage NSCLC is being evaluated so that clinical researchers can use the survival data from a pilot or Phase II regimen to help predict how likely it is that the new regimen will provide prolonged survival compared with standard chemotherapy in a prospective trial analogous to the model for small cell lung cancer. With increasing numbers of available therapeutic agents to choose from, and the vast numbers of potential combinations of these agents, it is hoped that the use of this model will offer a potential tool for clinical investigators to assess the likelihood that a pilot/Phase II chemotherapy regimen will prove superior to...
standard regimens and thereby be brought into clinical practice in a more prompt and efficient manner.

Materials and Methods

Phase III Trials. The Phase III trials for patients with advanced-stage NSCLC initiated from 1973–1994 were identified through a search of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) database, computer-based search of MEDLINE, and by direct contact with the Cooperative Groups [Cancer and Acute Leukemia Group B, Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group (NCCTG), Southeastern Oncology Group (SEOG), Southwest Oncology Group (SWOG), and National Cancer Institute of Canada-Clinical Trials Group]. A summary of these trials has recently been published (1).

Pilot and Phase II Trials. For each published Phase III trial of patients with advanced-stage NSCLC, we attempted to identify a pilot or Phase II study that preceded the randomized trial. A uniform search approach was used: (a) pilot studies were identified first through a review of published references; and (b) the authors and chairpersons of the lung committee of the cooperative groups were contacted to confirm the pilot study that gave rise to the randomized trial. Information was obtained on the dates of the pilot studies, the number of patients on study, the gender of patients, the treatment regimens used, response rates, median survivals, and the number of patient deaths in the pilot at the time of the analysis. Pilot or Phase II studies were included if the pilot was performed by the cooperative group that performed the subsequent trial, if the institution that performed the pilot was a participating member of the subsequent Phase III trial, or if the pilot regimen that was performed was analogous to the regimen tested in a subsequent cooperative group trial.

The Model. The statistical design of a randomized Phase III clinical trial is based on having adequate power to detect a clinical difference of interest. For example, one might assume that the distributions of survival duration are exponential in form with an 8-month median for the control group and 12-month median for the experimental group (4). The specification of the median for the control is based on the historical data from previous Phase III trials. On the other hand, because of the limited information about the experimental treatment, the specification of the median for the experimental group is usually hypothetical. Ideally, the experimental median should represent the smallest prolongation in survival that the investigators deem a medically significant improvement over present therapy.

In patients with extensive-stage small cell lung cancer, Chen et al. (3) developed a model to provide assistance in selecting chemotherapy regimens from Phase II studies for subsequent use in Phase III randomized studies. The model combines the past Phase III experience with the survival data from the Phase II study of the experimental regimen to calculate the expected power of the Phase III trial. This expected power can then be used in making the decision of whether the regimen warrants Phase III testing. Chen et al. suggested that an expected power of 0.55 or higher can be used as an indication for taking the regimen into Phase III testing.

The model assumes that survival times on the control (c) and experimental (e) arms follow exponential distributions with hazards , respectively. The exponential hazards and are modeled as random variables with parameters and . These parameters are used to formally incorporate into the model the information and uncertainty about the effectiveness of the experimental treatment. Parameter can be thought of as representing the total number of deaths. In a similar way, parameter corresponds to the inverse of total follow-up time and is derived to have the median survival at a specified value. On the basis of the control arms of the Phase III trials, we used , and .

For an experimental regimen, before the Phase II study, the probability of obtaining a positive result in a Phase III trial is set to 0.15 because only 5 (15%) of the 33 Phase III trials demonstrated a statistically significant improvement. We have specified these prior beliefs by setting and to give an expected median (m) approximately equal to that expected for the control treatment but with the probability that is greater than 8 months of 0.15 (a = 9 and 1/b = 68). These parameters are updated with the Phase II results in the following way:

where is the number of deaths observed in the Phase II trial. The parameter is updated as

is the sum of the survival times in months (till death or last follow-up) observed for patients in the Phase II trial. Expected power is defined as the probability of a significant result averaged with regard to the distributions of and . A detailed description of the calculation is given in Ref. (3).

Results

Phase III Trials. Thirty-three Phase III trials in patients with advanced-stage NSCLC initiated between 1973 and 1994 were identified (1). Only 5 (15%) of the 33 Phase III trials demonstrated a statistically significant difference between the experimental arm and the standard treatment (4–8). There was a modest trend toward prolongation in patient survival over the 22 years of the analysis (5.2 months in the 1973–1983 time period versus 5.8 months in the 1984–1994 time period). The median survival of patients treated on the control arms between 1973 and 1994 was 5.2 months.

Pilot/Phase II Studies. Nineteen pilot studies were identified that were subsequently studied in Phase III trials in patients with advanced-stage NSCLC (9–27). Data on either median survival (n = 3) or number of deaths (n = 5) were not available in eight of these pilot trials (19–26). Attempts to obtain the outstanding information on these pilot studies by direct contact with the primary investigator or the cooperative group were made, but were unsuccessful. One additional pilot study included patients with small cell lung cancer and, therefore, was excluded from the analysis (27).

The remaining 10 trials had complete information on response rates, median survival, and number of deaths in the pilot/Phase II studies that preceded the randomized Phase III trials (9–18). In 8 of the 10 pilot studies, all of the eligible patients were included in the analysis; in the remaining 2 studies, patients failing to complete the first treatment cycle were excluded. The pilot regimens and clinical outcomes are summarized in Table 1. A median of 51 patients were treated on each
of the ten pilot/Phase II study (range, 17–121). The median survival durations of patients treated in the pilot/Phase II studies ranged from 5.0 to 11 months. The expected power of the 11 associated Phase III trials are outlined in Table 2. There were four Phase II trials that gave expected power above the 0.55 threshold; three of them (16–18) were followed by Phase III studies that showed a statistically significant difference between the experimental and the control arm. The trial by Bitran et al. (9) gave expected power of 0.80 but the subsequent Phase III trial showed no statistically significant difference in survival between the two arms. None of the seven Phase III trials that followed Phase II trials with expected power below 0.55 showed significant differences in survival between the control and the investigational arms of the studies. Fig. 1 provides a graphical representation of the relationship between the expected power and the subsequent Phase III trial. It shows the hazard ratio (median survival of the experimental over the control arm, e.g., hazard ratio of 1.3 corresponds to a 30% increase in median survival) observed in the Phase III studies plotted against the expected power. The size of the circle representing each study is weighted by the number of deaths in the corresponding Phase II pilot study.

**Discussion**

This is the fourth report of an ongoing effort analyzing the clinical trials of extensive-stage small cell lung cancer as well as stages IIIB and IV NSCLC. We think that it is important to evaluate our records in clinical trials for patients with advanced lung cancer, to disseminate the findings, and to propose methods for improving the evaluation of regimens being tested in Phase II trials. The introduction of molecularly targeted agents that have the potential to cause stable disease if they have cytostatic rather than cytotoxic anticancer activity may make it important to be able to assess stable disease and survival in Phase II trials.

The single-agent Phase I trials of some of the molecular targeted therapies (ZD1839 and OSI-774) with information about patients with NSCLC have been published in journal article form in 2001 and 2002. These studies have documented stable disease for up to 1 year as well as responses in patients with relapsed NSCLC (28–30). However, the results of the Phase II and Phase III trials combining these targeted agents with cytotoxic chemotherapy have yet to be reported in article form. Applying the proposed model awaits the publication of the details of these Phase II and III investigations.

**Table 1** Pilot studies of regimens in patients with advanced-stage NSCLC

<table>
<thead>
<tr>
<th>Author: Phase III</th>
<th>Author: pilot study</th>
<th>No. of patients in pilot trial</th>
<th>Male/Female in pilot trial</th>
<th>Pilot regimen</th>
<th>Response rate CR* %</th>
<th>Response rate PR %</th>
<th>Median survival (months)</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruckdeschel et al. (13)</td>
<td>Bitran et al. (9)</td>
<td>54</td>
<td>Not stated</td>
<td>CAMP,</td>
<td>9</td>
<td>24</td>
<td>8.4</td>
<td>46</td>
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<td>Kris et al. (33)</td>
<td>Woodcock et al. (10)</td>
<td>27</td>
<td>25/2</td>
<td>VbP(120)</td>
<td>0</td>
<td>52</td>
<td>5.0</td>
<td>19</td>
</tr>
<tr>
<td>Dhingra et al. (35)</td>
<td>Hainsworth et al. (11)</td>
<td>92</td>
<td>70/22</td>
<td>VdEP</td>
<td>3</td>
<td>16</td>
<td>5.4</td>
<td>91</td>
</tr>
<tr>
<td>Krook et al. (36)</td>
<td>Butler et al. (12)</td>
<td>25</td>
<td>14/11</td>
<td>FAMI</td>
<td>4</td>
<td>32</td>
<td>6.5</td>
<td>21</td>
</tr>
<tr>
<td>Weick et al. (37)</td>
<td>Woodcock et al. (10)</td>
<td>27</td>
<td>25/2</td>
<td>VbP(120)</td>
<td>0</td>
<td>52</td>
<td>5.0</td>
<td>19</td>
</tr>
<tr>
<td>Veezer et al. (38)</td>
<td>Ruckdeschel et al. (13)</td>
<td>121</td>
<td>90/31</td>
<td>MIVbP</td>
<td>5</td>
<td>26</td>
<td>5.1</td>
<td>112</td>
</tr>
<tr>
<td>Goldberg et al. (39)</td>
<td>Krook et al. (14)</td>
<td>17</td>
<td>Not stated</td>
<td>E days 1, 2, 3/ P days 2, 3 (civi)</td>
<td>12</td>
<td>41</td>
<td>6.6</td>
<td>15</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Author: pilot study</th>
<th>Median survival in experimental arm in pilot study</th>
<th>No. of deaths</th>
<th>Expected power</th>
<th>Author: Phase III</th>
<th>Phase III study outcome</th>
<th>Median survival mo (Phase III studies)</th>
<th>Study vs. Standard</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitran et al. (9)</td>
<td>8.4</td>
<td>46</td>
<td>0.80</td>
<td>Ruckdeschel et al. (13)</td>
<td>4.4 vs. 5.1</td>
<td>Not significant</td>
<td></td>
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<tr>
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<td>5.0</td>
<td>19</td>
<td>0.15</td>
<td>Kris et al. (33)</td>
<td>12.3 vs. 8.5</td>
<td>0.176</td>
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<td>5.4</td>
<td>91</td>
<td>0.13</td>
<td>Dhingra et al. (35)</td>
<td>6.4 vs. 6.7</td>
<td>Not significant</td>
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<td>6.5</td>
<td>21</td>
<td>0.38</td>
<td>Krook et al. (36)</td>
<td>5.6 vs. 4.9</td>
<td>0.73</td>
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<tr>
<td>Woodcock et al. (10)</td>
<td>5.0</td>
<td>19</td>
<td>0.15</td>
<td>Weick et al. (37)</td>
<td>5.9 vs. 5.0</td>
<td>0.61</td>
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<tr>
<td>Ruckdeschel et al. (13)</td>
<td>5.1</td>
<td>112</td>
<td>0.07</td>
<td>Veezer et al. (38)</td>
<td>3.7 vs. 5.4</td>
<td>0.09</td>
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<tr>
<td>Krook et al. (14)</td>
<td>6.6</td>
<td>15</td>
<td>0.38</td>
<td>Goldberg et al. (39)</td>
<td>5.2 vs. 4.9</td>
<td>0.71</td>
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<tr>
<td>Gandara et al. (15)</td>
<td>6.8</td>
<td>51</td>
<td>0.47</td>
<td>Gandara et al. (40)</td>
<td>6.9 vs. 7.2</td>
<td>0.53</td>
<td></td>
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<tr>
<td>Depierre et al. (16)</td>
<td>7.6</td>
<td>69</td>
<td>0.69</td>
<td>Crawford et al. (15)</td>
<td>Positive</td>
<td>6.9 vs. 5.1</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Johnson et al. (17)</td>
<td>8.7</td>
<td>51</td>
<td>0.85</td>
<td>Bonomi et al. (4)</td>
<td>Positive</td>
<td>9.9 vs. 7.6</td>
<td>0.05</td>
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<tr>
<td>Berthaud et al. (18)</td>
<td>11</td>
<td>25</td>
<td>0.94</td>
<td>Wozniak et al. (8)</td>
<td>Positive</td>
<td>8.0 vs. 6.0</td>
<td>0.0018</td>
<td></td>
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</table>
Our model uses survival information from pilot or Phase II studies and, thus, is directly applicable to cytostatic agents. It can also be used with targeted therapy if only a subset of patients expresses the target. A further refinement of the model is possible in situations in which the target population can be identified prospectively; this is a subject of ongoing research. Therefore, testing of the model in these present trials may provide another useful instrument for investigators considering using cytostatic/targeted agents alone or in combination with other chemotherapeutic regimens in patients with advanced NSCLC and other malignancies. Further testing of this model in these ongoing trials may provide another useful instrument for investigators considering using cytostatic agents in combination with other chemotherapeutic agents in patients with advanced NSCLC and other malignancies. The model may also be adapted to other cancers (breast or prostate cancer), but we await the expertise of other investigators familiar with the trials to initiate these studies.

Novel therapeutic approaches in patients with cancer are assessed against accepted standard care in Phase III trials, as the accepted method of comparing treatments (31). However, Phase III trials require the participation of large numbers of patients and are associated with high financial costs in the provision of therapeutic agents, the performing of the clinical trial, data management, analysis of the data, and final publication of the results. Two recent articles assessed the trends in median survival of patients with advanced-stage lung cancer treated on Phase III trials in North America between the early 1970s and mid 1990s, one paper addressing patients with extensive-stage small cell lung cancer and the other in patients with advanced-stage NSCLC (1, 2). Unfortunately these reports reveal that 24% of the 21 Phase III trials in patients with extensive-stage small cell lung cancer, and only 5 (15%) of the 33 Phase III trials in patients with advanced-stage NSCLC, showed a statistically significant difference in median survival between the control regimen and experimental treatment arm(s). In view of this apparent difficulty experienced by clinical investigators in selecting which therapeutic agents to bring forward from pilot studies to produce superior results over standard therapy, a statistical model was developed for patients with extensive-stage small cell lung cancer (3). However, because NSCLC represents about 80% of lung cancer, the development of such a model in patients with NSCLC is all the more important, both in terms of the individual and in terms of the population as a whole. We have graphically presented only the expected power versus the hazard ratio of the trials. There was little relationship between the response rate and survival in the pilot/Phase II trials and the survival in the experimental arm of the Phase III studies (Pearson correlation <0.1) as was seen in the extensive-stage small cell lung cancer studies. The expected power of 0.55 segregated the advanced-stage NSCLC trials relatively well, analogously to the extensive-stage small cell lung cancer trials (3). Additional prospective trials will be needed to assess its utility for selecting regimens to take to Phase III trials.

Selection of the regimens for testing in Phase III trials has been primarily based on the Phase II response rate (32). There is an urgent need for improvement of this screening process, as evidenced by the 15% success rate in advanced NSCLC Phase III trials. We have evaluated whether the model of Chen et al. can aid in the selection of promising regimens in advanced-stage NSCLC. It is important to note that this model does not require that response be ignored but provides an additional tool for decision-making. Eleven Phase III studies in the advanced NSCLC have been initiated based on the promising response rates in the corresponding pilot Phase II studies. The use of the expected power criteria (with 0.55 threshold) to further refine regimen screening could have potentially resulted in three of four selected regimens showing significant improvement with no false negatives.

The expected power to predict whether a regimen that appears promising in a Phase II trial will be successful in a Phase III trial depends on the number of deaths observed in the Phase II trial and the median survival observed. Fig. 2 illustrates the relationship among the expected power, the number of events (deaths), and median survival. Each line shows the expected power as a function of median survival observed in the Phase II trials for a different number of deaths. Small trials with fewer than 30 patients (25 events) may not provide adequate information for assessing the regimen activity. For example, a regimen evaluated in a Phase II trial with 50 events and 8-month median survival has an expected power of 0.80, whereas the same regimen tested in a small trial with 10 events and the same median survival has an expected power of <0.5.

However, the model has potential limitations. The pilot study by Bitran et al. (9) had an expected power of 0.80 but failed to produce a statistically significant increase in survival when assessed in the subsequent Phase III trial reported by Ruckdeschel et al. (Ref. 13; median survival, 4.4 versus 5.1 months, study regimen versus control, respectively; P, not significant). The median survival in the pilot study (8.4 months) was nearly twice as long as was produced in the subsequent Phase III trial (4.4 months) and was responsible for the inflated expected power generated by our statistical model. Differences in patient selection, treatment regimens, and supportive care are
unaccounted for when data from a present treatment regimen is compared with historical data based on previous regimens.

The unexpected and unreported 2-fold excess in difference in median survival between the pilot study reported by Woodcock et al. (Ref. 10; median survival, 5.0 months) and the associated Phase III study by Kris et al. (Ref. 33; median survival, 12.3 months) is unexplained. However, because there were only 19 deaths within the pilot at the time of publication, the ability of the model to predict whether this regimen is of potential therapeutic value over existing standards is severely limited, as outlined above (10). The exceptional median survival of 12.3 months in patients treated on the vinblastine/cisplatin arm of the Phase III trial has not been repeated and may reflect the mere total of 48 patients (vindesine/cisplatin) and 49 patients per treatment arm (vinblastine/cisplatin). These combined factors of low patient numbers in the pilot and subsequent Phase III trial are recognized as potential confounders for our proposed model.

The early randomized Phase III studies for patients with advanced NSCLC often did not have an identifiable preceding Phase I or II pilot trial, or the information reported in such a trial was inadequate to use in our analyses. Sixteen of the 33 Phase III randomized studies of patients with NSCLC were initiated between 1973 through 1980 (1). Seven did not have an identifiable pilot study, and eight did not have information on the number of deaths or median survival. Only a single study had the information necessary in this proposed model (9). Ten of the 11 studies with adequate information for use in our model were initiated in the later trials starting between 1981–1993 (Table 2). Recommendations for reporting clinical trials were not made until 1983 so that data on median survival and number of deaths were not often present in the reports (34). This deficit in reporting data in Phase II trials has improved, and the information needed for the model is typically reported in the articles published on the Phase II trials. Therefore, there exists a potential for bias in the methodology and quality of the obtained data in this model toward using only data from later trials. However, the main goal of the proposed model is to streamline clinical development of new anticancer therapies by refining the efficiency of regimen selection. It is not designed as an independent summary of drug activity but rather as another aid in assessing the efficacy of regimens in Phase I and II trials.

The validity of this statistical model and its usefulness in helping investigators decide which regimens to bring forward to Phase III trial in patients with advanced-stage NSCLC can be verified by future prospective studies. We would predict that regimens with an expected power of >0.55 are most likely candidate regimens for further evaluation in the Phase III setting. We await its prospective testing in clinical trials. The use of this model may expedite the development of regimens likely to present clinical advantage and to direct investigators away from pursuing regimens unlikely to produce a therapeutic benefit.

References

9. Bitran, J. D., Desser, R. K., DeMeester, T., and Golomb, H. M. Metastatic non-out-cell bronchogenic carcinoma. Therapy with cyclo-

Fig. 2 Plots of the expected power based on the median survival and number of deaths of patients in Phase II trials. X-axis values, the median survival of patients with advanced-stage NSCLC treated in the Phase II studies. Y-axis values, the expected power of the subsequent Phase III trial to show a difference between the Phase II regimen and standard chemotherapy. Each curve differs on the basis of the number of patients’ deaths (events) that have been observed in the Phase II study. Each Phase II study; the size of the circle is proportional to the number of deaths observed in the corresponding Phase II pilot study.


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