Review

Paclitaxel-based therapy in non-small-cell lung cancer: Improved third generation chemotherapy

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Summary

The newer or ‘third generation’ chemotherapeutic agents (paclitaxel, docetaxel, vinorelbine, gemcitabine, irinotecan, topotecan) have all recently been shown to have substantial activity against non-small-cell lung cancer (NSCLC). Many of these agents are now being incorporated into the therapy for patients with advanced disease. Paclitaxel was the first ‘third generation’ drug to be studied. The use of paclitaxel and carboplatin has proven to be a well tolerated and quite active regimen with one-year survival in patients with stage IV disease of about 40% and two-year survival of about 20%. These survival rates are at least twice as good as previous platinum-based regimens. We have simplified the administration of paclitaxel by using a one-hour infusion and many other investigators and clinicians have followed suit. The results are equivalent to a three-hour infusion schedule. Given the degree of activity in patients with stage IV disease, it is imperative to begin neoadjuvant and adjuvant trials with the newer drugs and drug combinations. We and others have started a neoadjuvant strategy which has proven to be feasible and most patients tolerate surgery well. While the results are quite preliminary, we have seen some complete pathologic responses (about 20%) and are encouraged by these early data. In addition, we have routinely used adjuvant paclitaxel and carboplatin in patients with stage IB-IIIA disease who have been previously resected. Radiotherapy and a weekly schedule of paclitaxel and carboplatin have been incorporated for patients with stages II-IIIB (selected IIIB patients). Randomized comparisons are certainly needed in the neoadjuvant and adjuvant arena and the other ‘third generation’ drugs need to be quickly evaluated. We have chosen to add a third agent to paclitaxel and carboplatin. The evaluation of several triple combinations including the addition of gemcitabine, vinorelbine and topotecan, respectively to the paclitaxel–carboplatin combination has been completed. Preliminary results from these trials will be briefly summarized and plans for additional studies of the newer agents will also be discussed. Studies to learn the appropriate combinations, doses and schedules of the newer drugs in concert with radiotherapy and/or resection are also urgently needed. Since the newer ‘third generation’ drugs appear to genuinely improve the survival of patients with stage IV disease, it is likely that incorporation of these more active agents into therapy for lower stages of disease will make an even greater impact on overall survival for patients with this common neoplasm.

Key words: non-small-cell lung cancer, paclitaxel

Introduction

Several new chemotherapeutic agents have recently made an impact on survival for patients with advanced, (stage IIIB and stage IV) non-small-cell lung cancer. I anticipate that this impact will be even more important for patients with earlier stage disease. The recent improvement is due to several new drugs which have activity against non-small-cell lung cancer. These include paclitaxel, vinorelbine, docetaxel, gemcitabine and irinotecan.

I consider these new drugs as third generation chemotherapy for non-small-cell lung cancer [1]. This designation is warranted at this time and helps place the brief history of systemic therapy for non-small-cell lung cancer in perspective. The first generation group of drugs (alkylating agents, antimetabolites, anthracyclines and early vinca alkaloids) made a major impact for patients with several types of malignancies, particularly leukemia, Hodgkin’s disease, non-Hodgkin’s lymphomas, breast cancer and several childhood cancers. However, these same agents were relatively inactive in non-small-cell lung cancer and had no effect on the survival of the patients and only rarely produced transient palliation either as single agents or in combinations. The second generation group of drugs heralded by cisplatin, alone or in combination with alkylating agents, etoposide, vinca alkaloids, mitomycin and other drugs have had a small, but real, impact on the survival of patients with stage IV disease [2–6]. More importantly, when combined with radiotherapy, patients with unresectable stage III disease have had a statistically significant prolongation of survival compared to radiotherapy alone [1, 7–12]. Furthermore, for selected patients with resectable stage IIIA, the pre-operative chemotherapy with the second generation cisplatin-based chemotherapy has made an important impact on survival compared to surgery alone [13, 14].

The third generation drugs are more active than second generation agents, and more importantly, as
single agents and in combination with other drugs, they significantly improve the one year and probably the two year survival in the worst group of patients (i.e., those with stage IV disease) [1]. These data continue to evolve and over the next several years, we should have a better understanding of the toxicity of the third generation agents, their appropriate use in combination chemotherapy as well as their incorporation into combined modality programs for patients with earlier stage disease (stages I–III).

Contributions of second generation chemotherapy

The development of cisplatin and cisplatin-based combination chemotherapy, included about 15 years of intensive clinical research and was accompanied for many of these years by an intensive controversy regarding the value of this chemotherapy for patients with stage IV disease. There was a fairly strong consensus that first generation chemotherapy produced no effect on the survival for these patients. Multiple randomized studies utilizing cisplatin-based chemotherapy (second generation therapy) versus best supportive care, eventually and definitively demonstrated a modest survival effect for patients with stage IV disease [6] (survival at one year, about 20%–25% versus 5%–10% with best supportive care only). Second generation chemotherapy was superior to no therapy at all and therefore was also superior to first generation therapy.

The impact of second generation chemotherapy has been far greater in patients with stage III disease. These data supporting important survival benefits for unresectable stage III patients have come from multiple randomized comparisons of second generation chemotherapy plus radiotherapy compared to radiotherapy alone, either concurrently or sequentially. The five year survival rate is about four times as long (20% versus 5%) [12]. It is now universally accepted that good performance status patients with unresectable stage III disease benefit by the use of second generation cisplatin-based chemotherapy plus radiation.

Very few definitive studies have evaluated second generation chemotherapy in patients with even earlier stage (I, II, resectable III) disease. Two important exceptions have been reported from Spain [13] and the US [14]. These trials included patients with resectable stage IIIA non-small-cell lung cancer. In both studies, patients randomly received either second generation cisplatin-based chemotherapy preoperatively for three courses or immediate surgical resection. In both of these studies, the preoperative or neoadjuvant, second generation chemotherapy followed by resection was superior to resection alone. The three-year survival rates were 26% versus 0% [13] and 56% versus 13% [14], respectively. Although these studies were relatively small containing only a total of about 60 patients each (30 in each arm), the survival differences were impressive enough that both studies were stopped prematurely. These encouraging results highly suggest that third generation chemotherapy, which is superior to second generation chemotherapy, will indeed result in an even more profound effect on the survival for these patients with earlier stage disease. These studies are eagerly awaited.

Development of paclitaxel as a third generation chemotherapeutic agent

Paclitaxel and vinorelbine have thus far been studied more, and therefore more data is available to review in documenting the recent achievements in systemic chemotherapy. Vinorelbine is superior to vindesine, a second generation vinca alkaloid, in the treatment of patients with stage IV disease [15]. Vinorelbine plus cisplatin is superior to cisplatin as a single agent [16]. The relatively mild toxicity and ease with which vinorelbine combines with other agents make it a promising third generation drug. Studies are currently in progress evaluating an equally promising drug, gemcitabine, as well as docetaxel. Single agent trials [1, 17] suggest these drugs are superior to second generation combination chemotherapy. About 30%–40% of treated patients were alive after one year. Further studies are in progress. Paclitaxel is an impressive drug, and many of the recent achievements in therapy can be attributed to the development of this drug. I will briefly review the current role of paclitaxel and speculate on the promising future of this drug for patients with earlier stage disease.

In the US, paclitaxel was first tested in a phase II trial utilizing a randomized design against two other phase II agents [18]. In this original small trial, paclitaxel was active (21% response rate) but the other two phase II drugs were inactive. The one year survival for the patients receiving paclitaxel was 40% compared to less than 10% for the two inactive drugs. Two year survival was near 20% and a confirmatory phase II trial showed nearly identical results [19, 20]. These studies set the stage for several other phase II trials of various doses and schedules, as well as combination regimens including paclitaxel. The combination of paclitaxel plus cisplatin (the single agent standard bearer of second generation chemotherapy) was tested by the Eastern Cooperative Oncology Group (ECOG) in a large, prospective, randomized, phase III trial, comparing this combina-

Table 1. Randomized prospective phase III trials of US cooperative groups.

<table>
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<tr>
<th>SWOG</th>
<th>ECOG</th>
<th>CALGB</th>
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<tr>
<td>Paclitaxel-carboplatin vs. vinorelbine-cisplatin</td>
<td>Paclitaxel-carboplatin vs. paclitaxel-cisplatin</td>
<td>Paclitaxel-carboplatin vs. docetaxel-cisplatin</td>
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Abbreviations: SWOG – Southwest Oncology Group; ECOG – Eastern Cooperative Oncology Group; CALGB – Cancer and Acute Leukemia Group B.
tion with a standard cisplatin–etoposide regimen [21]. This was a three-arm trial, with two arms including paclitaxel and cisplatin, one with higher dose paclitaxel (250 mg/m²) and G-CSF and the other with low-dose paclitaxel (135 mg/m²) without G-CSF. In both instances, paclitaxel was given over 24-hour infusion. This definitive trial showed a statistically significant increase in the response rate and the survival of the paclitaxel–cisplatin combination. There was no advantage of high-dose paclitaxel in this 24-hour infusion. Recent data highly suggest when given as a short infusion (three hours), a higher dose (225 mg/m²) is superior to a lower dose (175 mg/m²) (Dr P.A. Kosmidis, personal communication, Hellenic Cooperative Group, 20 March 1998).

At about the same time that the large ECOG study first began, several phase II trials were initiated with paclitaxel plus carboplatin in stage IIIIB–IV patients [22–24]. Carboplatin, less toxic than cisplatin, with no apparent loss in efficacy, combined extremely well with paclitaxel. These phase II trials showed surprising tolerability, a platelet sparing effect and response rates ranging from 25% to 55%. Even more important, these trials have consistently been associated with a one-year survival rate of about 40%. Two year survivals have yet to be reported in most trials, but in at least one large trial, it has been approximately 20% [25]. The combination of paclitaxel and carboplatin is very popular and represents one of the treatments in all three large randomized prospective phase III trials now being conducted by the major cooperative groups in the US (Table 1). In addition, the European Organization for the Research and Treatment of Cancer is comparing paclitaxel–carboplatin to paclitaxel–cisplatin. The favorable toxicity profile will likely make the combination of paclitaxel and carboplatin the preferable therapy.

The lack of severe myelosuppression in most patients receiving paclitaxel and carboplatin has prompted us to study this two-drug combination with the other new drugs in patients with stages IIIIB–IV. A phase I–II trial has been completed with gemcitabine added as a third drug. The maximum tolerated doses were: paclitaxel 200 mg/m² day 1; carboplatin AUC = 5 day 1; gemcitabine 1000 mg/m² days 1 and 8. This regimen was reported every three weeks. Although there was more neutropenia and thrombocytopenia compared to paclitaxel and carboplatin, there was no increased evidence of neutropenic fever, bleeding, or treatment-related death. The response rate was 48% and one year survival was 45%. This is a promising three-drug combination and will be compared in a large study to paclitaxel and carboplatin.

We are also studying the addition of vinorelbine and topotecan to the paclitaxel and carboplatin combination. These phase I–II studies are currently in progress. Should these triplet combinations prove superior, they could be used in patients with earlier stage disease.

A few phase II trials have also looked at the feasibility and toxicity of paclitaxel and a platinum agent in patients with stage III disease [1, 26]. These early trials often combined paclitaxel with cisplatin with our without etoposide and more recently carboplatin. Other phase II studies with concurrent or sequential radiotherapy are in progress. Paclitaxel has been used as a ‘radiosensitizer’ in low-dose weekly schedules with concurrent radiotherapy [27]. Carboplatin has also been added to this regimen [28, 29]. Although associated with substantial esophagitis, the results of these phase II trials look very encouraging with median survivals and one-year survivals comparing favorably to results with second generation chemotherapy with radiotherapy. Prospective randomized phase III comparisons are now considered a priority.

Although paclitaxel combinations, or other third generation drugs, have not yet been proven to be superior to second generation chemotherapy for patients with stage III disease, it would be surprising if this were not the case. Response rates are inversely related to the stage of disease for patients with non-small-cell lung cancer. The one-year survival of the patients with the worst prognosis, those with stage IIIIB and IV disease, has been doubled from 20% to 40% with paclitaxel and paclitaxel-based combination chemotherapy. Therefore, it would be expected that these results would translate to even greater survival benefits for patients with earlier stages of disease. Phase II pilot or feasibility studies utilizing paclitaxel and carboplatin in the neoadjuvant or adjuvant setting are in progress for patients with stages IB–II disease and stage IIIA disease (Tables 2 and 3). Randomized prospective phase III trials comparing these approaches versus surgery alone are likely to begin very soon.

### Summary of achievements of chemotherapy for non-small-cell lung cancer

In the last few years, a new generation of chemotherapy, third generation chemotherapy, is now being actively

### Table 1. Cooperative university medical centers neoadjuvant phase II trial in early non-small-cell lung cancer.

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<tr>
<th>Stage</th>
<th>Mediastinal nodes negative</th>
<th>Biopsy required</th>
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<td>T2N0</td>
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### Table 2. Sarah Cannon–Minnie Pearl Cancer Center neoadjuvant phase II trial in early non-small-cell lung cancer.

- Stages IB, IIA, IIB, IIIA – biopsy of regional nodes not required
- Stage IB–II: Mediastinal nodes negative
- Stage IIB–IV: Mediastinal nodes positive
- Stage IIIA: Mediastinal nodes negative

### Table 3. Surgical resection

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<tr>
<td>Surgical resection</td>
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<td>Three courses post-operative paclitaxel–carboplatin</td>
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applied in patients with non-small-cell lung cancer. Many studies are in progress. Even at this early stage of development, data show third generation chemotherapy is superior to second generation chemotherapy for patients with stage IV disease. We have had ample data showing that second generation chemotherapy is superior to first generation chemotherapy, which had no effect on the survival for patients with stage IV disease, or for that matter, in any stage of disease. Second generation chemotherapy will no longer be commonly used for patients with non-small-cell lung cancer. However, these cisplatin-based regimens did modestly improve the survival of patients with stage IV disease and made a substantial impact for those with stage III disease when used concurrently or sequentially with radiotherapy. There is every reason to now speculate that the third generation therapies as represented by paclitaxel and paclitaxel-based chemotherapy will make an even more important impact on survival for patients with all stages of non-small-cell lung cancer, but particularly for those patients with stages IB–IIIA disease. Within the next five years, we should have sufficient data from studies to substantiate or refute this speculation.

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References


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