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ORIGINAL ARTICLE

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High-dose carboplatin plus paclitaxel with granulocyte colony-stimulating factor and peripheral blood stem-cell support in non-small-cell lung cancer

Abstract The treatment of non-small-cell lung cancer (NSCLC) has recently undergone major changes due to the availability of new drugs that demonstrate substantial activity in NSCLC patients. Although cure for the majority of stage III NSCLC and effectively all stage IV disease patients remains rare, a number of compounds, including carboplatin, paclitaxel, docetaxel, irinotecan, and vinorelbine, have proved useful in the treatment of these patients. Together with a number of phase II trials, phase I trials utilizing escalating doses of carboplatin and paclitaxel with growth factor or growth factor and blood stem-cell support have shown that substantial increases in dose intensity can be achieved. These studies in small numbers of patients have demonstrated that these regimens have encouraging activity and have formed the basis of a Cancer and Leukemia Group B (CALGB) phase II pilot study. This study will utilize two cycles of high-dose carboplatin and Taxol given at an AUC dose of 18 and a 24-h infusion dose of 250 mg/m^2, respectively, with growth factor and stem-cell support to treat stage III NSCLC patients. Patients will also receive multimodality therapy, including radiation with or without surgery. It is hoped that this effort to intensify treatment in patients with limited-stage disease will improve survival and benefit the large number of patients with stage III tumors. This paper outlines the phase I results that formed the basis of the CALGB trial and reviews several recent reports of phase II or phase III trials of single-agent and combination regimens for NSCLC.

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Introduction

Standard therapy for patients with advanced non-small-cell lung cancer (NSCLC) has consisted of either supportive care or a combination of cisplatin or carboplatin and a second agent such as vinblastine, vindesine, or etoposide. Although these regimens have been shown to improve the quality of life and, in responding patients, the duration of survival, treatment remains unsuccessful in the majority of cases and has been shown to produce durable responses only rarely [3, 15, 18, 20, 21, 32, 36, 42]. Efforts to improve these outcomes using high-dose chemotherapy have been generally unrewarding, and only with the recent advent of several new agents have a high frequency of response and survival exceeding 1 year been observed [1, 6, 8, 11–14, 16, 17, 22, 26, 29, 30, 40, 43].

In contrast to patients with metastatic disease, there has been a clear improvement in survival, and cure rates approaching 20% have been observed in patients with stage III disease who have received combination treatment with chemotherapy and surgery or involved-field radiation (Table 1) [9, 27, 28, 31, 33, 34, 37]. Trials such as that reported by Dillman and the Cancer and Leukemia Group B (CALGB) investigators [9] have demonstrated that 2 cycles of standard-dose cisplatin and vinblastine followed by radiation therapy produce improved survival rates compared to radiation alone. Thus, unlike patients with metastatic disease, patients with stage III disease have benefited in terms of both response rate and survival following the administration of only two cycles of standard-dose chemotherapy. Although not all of these studies have been positive [28], there is reason to believe that novel approaches that include new drugs or intensive doses of active agents might be more effective in patients with limited disease than in those with more advanced cancers.

Table 1 Disease-free or overall survival as determined in NSCLC patients undergoing radiation therapy or surgery with or without chemotherapy (*XRT* Radiation therapy)

Modality	Survival (%)		*P*	Reference
	Chemotherapy	No chemotherapy		
XRT	23	11	0.04	[9]
XRT (3-year disease-free survival)	16	2	0.048	[37]
XRT (5-year disease-free survival)	5	7	0.2	[28]
Surgery (3-year overall survival)	56	15	0.018	[34]
Surgery (2-year disease-free survival)	30	0	0.001	[33]

Table 2 Recent studies of single-agent chemotherapy in advanced NSCLC

Agent	Dose/m²	Number of patients	Response rate (%)	Reference
CPT-11	100 mg q week	72	32	[12]
Docetaxel	100 mg q 3 weeks	44	21	[11]
Edetrexate	80 mg q week×5	19	30	[22]
Gemcitabine	800 mg q week×3	29	24	[1]
Navelbine	30 mg q week	72	29	[8]
Navelbine	25 mg q week	87	36	[43]
Paclitaxel	250 mg q 3 weeks	24	21	[6]
Paclitaxel	200 mg q 3 weeks	25	24	[29]
Paclitaxel	200 mg q 3 weeks	53	25	[17]
Paclitaxel	200 mg q 3 weeks	12	42	[40]
Topotecan	1.5 mg q 3 weeks	40	15	[31]

New agents in NSCLC

In a number of phase I and II trials, both single agents and combinations of drugs such as carboplatin and paclitaxel have been given at conventional doses to patients with advanced NSCLC. These reports have established the activity of these compounds for patients with stage III and IV disease [1, 3, 6, 8, 11, 12, 15, 17, 18, 20–22, 26, 29, 32, 36, 40, 42, 43]. In trials of single-agent carboplatin, response rates of 9–20% were achieved with modest toxicity [3, 15, 18, 20, 21]. In a trial by the Eastern Cooperative Oncology Group (ECOG), carboplatin produced a response rate of only 9% but yielded the longest median survival of all agents tested in a population of patients of advanced disease [3]. Subsequent trials with single-agent paclitaxel [6, 29, 40, 43] have produced response rates of 16–42%, with 41% of the patients enrolled in the trial by Chang et al. [6] surviving beyond 1 year and a median survival of 24 weeks (Table 2).

Other compounds that have shown activity in advanced NSCLC include edetrexate [22], docetaxel, topotecan, camptothecin derivatives such as CPT-11, and vinorelbine [7, 8, 11, 12, 17, 22, 23, 26, 39, 43]. The antitumor activity, combined with a relative lack of serious toxicity and the ease of administration, have contributed to a favorable cost-effectiveness study of vinorelbine in advanced NSCLC patients; these characteristics have also allowed vinorelbine to be added to other agents such as cisplatin or 5-fluorouracil (5-FU) without significant complications or compromise in the dose [7, 23, 39]. Cisplatin and vinorelbine combination therapy has been shown to produce an improved quality of life and a survival advantage as compared to vindesine and cisplatin or 5-FU and leucovorin combination therapy. The Southwest Oncology Group (SWOG) is currently comparing cisplatin and vinorelbine combination therapy with cisplatin and paclitaxel combination therapy. Although none of these new agents appears to be more active than single-agent pacitaxel, more definitive comparisons are required in studies such as that being undertaken by SWOG.

Studies under way with carboplatin and paclitaxel in advanced NSCLC

These encouraging results and the acceptable toxicity profiles of single agents have led to a number of combination studies using carboplatin and paclitaxel in advanced disease. In the largest series reported to date, Langer and colleagues [25] achieved a 64% response rate and a 54-week median survival. This is one of the few trials in advanced NSCLC in which the median survival has exceeded 50% at 1 year. Johnson et al. [19], Vafai et al. [41], Rowinsky et al. [35], and other investigators [2, 25] have reported response rates of 25–50%, although generally with one-year survival rates lower than those reported by Langer et al. [25] (Table 3). Other taxane combinations including docetaxel and cisplatin have also been reported [24]. On the basis of the encouraging phase II data, a trial comparing standard doses of carboplatin and paclitaxel with cisplatin and etoposide, one of the regimens most commonly used in the United States to treat advanced NSCLC, was recently sponsored by Bristol Myers-Squibb. This randomized study has recently completed accrual, but the results have yet to be published.

Dose escalation in NSCLC

The role of chemotherapy dose escalation in the treatment of advanced NSCLC remains to be demonstrated. A number of trials have failed to reveal any advantage for higher doses of cisplatin, carboplatin, or other compounds in this population of patients with metastatic disease [13, 14, 16, 30, 42]. Although no randomized comparison of different doses of carboplatin has been undertaken in this patient population, a phase III trial by Gandara and colleagues [14] reported no advantage for 200 mg/m² as compared to 100 mg/m² cisplatin when these agents were given as single agents or in conjunction with mitomycin C to 323 evaluable patients with stage IV disease.

The majority of phase II trials using the combination of carboplatin and paclitaxel have identified doses that range

Table 3 Combination regimens with cisplatin or carboplatin and paclitaxel (Taxol) or docetaxel

Agents (dose mg/m²)	Number of patients	Response rate (%)	Reference
Cisplatin (100–125) + paclitaxel (135–225)	29	38	[2]
Carboplatin (AUC 6) + paclitaxel (150–250)	27	63	[41]
Carboplatin (AUC 7–9) + paclitaxel (175–225)	17	50	[35]
Carboplatin (AUC 7.5) + paclitaxel (135–215)	54	62	[25]
Carboplatin (AUC 6) + paclitaxel (135–175)	51	27	[19]
Cisplatin (100) + docetaxel (100)	24	25	[24]

between a carboplatin AUC dose of 6-8 mg/m² and 175–250 mg/m² paclitaxel. Higher doses of both carboplatin and paclitaxel can be given with cytokine or blood stem-cell support, and in a phase I study with a carboplatin AUC dose of up to 20 mg/m² and a paclitaxel dose of 250 mg/m², six of seven patients with advanced-stage NSCLC responded to these high drug doses [5]. Although the highest response rates in the conventional-dose trials have been obtained with paclitaxel doses of ≥200 mg/m², a recently reported phase III trial comparing the combination of cisplatin and escalating doses of paclitaxel did not support this finding [38]. In a trial reported by Bonomi and investigators from the ECOG [4], no significant difference in response rate, response duration, or survival was found between a fixed dose of cisplatin coupled with 24-h infusions of either 135 or 250 mg/m² paclitaxel. This trial used cisplatin rather than carboplatin, but the results nevertheless underscore the importance of randomized trials in establishing standards of care.

High-dose therapy with carboplatin and paclitaxel

In 1993, we initiated a phase I trial designed to identify the maximum tolerated doses (MTDs) of paclitaxel and carboplatin when given with peripheral blood stem-cell (PBSC) and granulocyte colony-stimulating factor (G-CSF) support [38]. This program sought to build on an earlier trial that had demonstrated the importance of PBSCs in abrogating the myelosuppression associated with administration of multiple cycles of single-agent high-dose carboplatin [38a]. It was also designed to follow the models that have evolved for diseases such as Hodgkin's and non-Hodgkin's lymphoma and testis, limited-stage small-cell lung, and ovarian cancers, all of which require more than a single cycle of effective therapy to achieve cure.

Patients with incurable and unresectable malignancies were eligible for enrollment. Requirements for treatment included a performance status of 0–2, liver function tests $<4\times$ normal, creatinine clearance >50 cc/min, a WBC of >3000/ml, a platelet count of $>1.1\times10^5$/μl, a bone marrow biopsy with $<25\%$ tumor cells, and no prior chemotherapy or serious underlying medical problems. Age limits were not specified.

After informed consent had been obtained, a central venous pheresis catheter was inserted and 10 μg/kg filgrastim (G-CSF) was given s.c. daily for 7 days. PBSCs were collected, frozen, and stored in liquid nitrogen. Following a minimum of 48 h, patients received decadron, diphenhydramine, and ranitidine as hypersensitivity prophylaxis and were admitted to the General Clinical Research Center, University of North Carolina at Chapel Hill. They then received a 24-h infusion of 250 mg/m² paclitaxel and a 1-h carboplatin infusion at escalating doses using the Calvert formula for AUC dosing [4]. Carboplatin dosing began at an AUC of 8 and increased in increments of 2. PBSCs collected after G-CSF mobilization were reinfused at 2 days after the completion of the first course of chemotherapy. Additional pheresis procedures were undertaken following recovery from the first cycle of chemotherapy, and these PBSCs were stored for reinfusion after each of the second, third, and fourth cycles of chemotherapy, which were given every 21 days.

This program achieved a dose escalation of carboplatin and paclitaxel that was several-fold higher than standard by combining G-CSF and PBSC support. As mentioned above, the MTD included a paclitaxel dose of 250 mg/m² given by 24-h infusion and a carboplatin AUC dose of 18. With this regimen we were able to deliver four cycles of therapy to the majority of patients without significant cumulative hematologic toxicity. Approximately 20% of treatment courses required hospitalization for fever and neutropenia, and patients required an average of 1.5 units of packed red blood cells and <1 unit of platelets per cycle at the MTD. The dose-limiting toxicities included one case of severe, transient, nephrogenic diabetes insipidus and one case of prolonged (beyond 14 days) neutropenia at an AUC of 20. Other serious side effects included several cases of grade 2 and 3 neurotoxicity, two cases of grade 3 diarrhea, and one case of grade 3 mucositis. With additional follow-up, several of these patients have shown a substantial improvement in neurotoxicity.

A similar study has been reported by Fennelly and colleagues, Memorial Sloan Kettering Cancer Center (MSKCC; New York, N.Y., USA), in patients with ovarian cancer [10]. They have developed a regimen that includes a single cycle of cyclophosphamide and paclitaxel for cytoreduction and stem-cell mobilization. PBSCs collected after this cycle are used along with G-CSF to support three cycles of carboplatin and paclitaxel given at doses of AUC 15 and 250 mg/m², respectively, followed by a single cycle of high-dose melphalan (140 mg/m²). This program has been used to form the basis of a Gynecologic Oncology Group trial as initial therapy in women with optimally debulked ovarian cancer. This pilot trial has recently opened at MSKCC, University of North Carolina at Chapel Hill, Fox Chase Cancer Center (Philadelphia, Pa.), and Washington University (St. Louis, Mo., USA).

Future directions

It is noteworthy that the randomized studies of dose escalation in NSCLC have been uniformly unsuccessful in patents with metastatic or advanced stage III disease. In addition to the inherent chemotherapy resistance demonstrated by these tumors, other factors that may contribute to these poor results include the debilitated state of many of these patients at presentation and the bulk of their tumors, which is associated with a greater likelihood of resistant cells. Such factors may preclude the observation of benefit from more intensive and toxic regimens. If this is the case, then one might expect that a more aggressive approach would be more effective in patients with less advanced tumors. Following the observation of acceptable toxicity and response in the advanced NSCLC patients enrolled in the high-dose University of North Carolina phase I trial, the CALGB has initiated a phase II pilot trial utilizing this intensive regimen in patients with initially unresectable stage III cancer. This trial will enroll previously untreated patients, who will undergo filgrastim-stimulated blood stem cell mobilization and pheresis followed by an initial 3-h infusion of 250 mg/m^2 paclitaxel followed by carboplatin given at an AUC dose of 18 over 1 h. Blood stem cells will be reinfused following chemotherapy and a second, identical cycle of treatment will be carried out following recovery of blood cell counts. After the completion of two cycles, patients will undergo restaging studies and tumor resection if they have had a substantial response and are deemed operable. All patients will proceed to involved-field radiation to optimize local control either following recovery from surgery or, if their disease remains unresectable, immediately after the second cycle of chemotherapy. The goal of the study is to achieve at least a 60% clinical response rate and a 20% rate of pathological complete responses.

These studies are intensive and expensive but hold the promise of substantially improving the results of therapy for patients with these routinely fatal diseases. Whether this proves to be the case, and at what cost, will be determined by phase II and, if warranted, phase III trials based on developmental studies such as those described herein.

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