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Phase II trial of edatrexate plus carboplatin in metastatic non-small-cell lung cancer: a Southwest Oncology Group study

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Abstract *Background*: Edatrexate and carboplatin are each active single agents in the treatment of non-small-cell lung cancer (NSCLC). Preclinical studies in NSCLC lines have demonstrated schedule-dependent synergy of edatrexate followed by carboplatin. In a phase I trial, we demonstrated the tolerability of this combination, the ability of ice-chip cryotherapy to ameliorate dose-limiting mucositis, and promising activity in NSCLC. This phase II trial (SWOG 9207) was undertaken to investigate the efficacy of this regimen in stage IV NSCLC. *Methods*: A total of 24 patients with stage IV disease were accrued to this Southwest Oncology Group (SWOG) multicenter study. Treatment consisted of edatrexate 80 mg/m^2 (50% dose on day 8) intravenously weekly for 5 weeks, then every other week, and carboplatin 350 mg/m^2 every 28 days. *Results*: Of the 24 patients, 23 were assessable for toxicity and response; one was ineligible for study entry. Myelosuppression was the most significant toxicity; grade 3–4 neutropenia was seen in 8/23 patients. Two patients died of neutropenic sepsis during the first cycle of therapy, in both instances associated with the presence of pleural effusions. Although mild mucositis was common, it was dose-limiting (grade 3) in only three patients. Objective response was observed in 3/23 patients (13%). The median survival time was 7 months, and 30% of patients remained alive at one year. *Conclusions*: This study suggests that ice-chip cryotherapy is effective in reducing the severity of mucositis typically associated with this edatrexate schedule of administration. However, unexpectedly severe myelosuppression resulted in death from neutropenic sepsis in two patients with third space fluid collections, leading to a protocol amendment to exclude such patients from study entry. Furthermore, response and median survival with this dose schedule of edatrexate and carboplatin do not appear to be improved compared to other chemotherapeutic regimens tested by SWOG in this patient population.

Key words Edatrexate · Carboplatin · Non-small-cell lung cancer

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Introduction

Recent studies and meta-analysis support the use of platinum-based chemotherapy in the treatment of metastatic non-small-cell lung cancer (NSCLC). These studies demonstrate palliation of symptoms, improved median survival, and increased numbers of survivors at 1 year compared to patients receiving best supportive care [2, 4, 13, 18, 21]. Nevertheless, the overall therapeutic impact remains modest, and virtually all patients with stage IV disease eventually die of progressive disease. New effective drugs and less toxic combination regimens are clearly needed. Edatrexate (10-ethyl-10-deazaminopterin, 10-edam) is an analog of methotrexate with single-agent activity in NSCLC [7]. Edatrexate has several potential advantages over methotrexate, including increased intracellular transport, increased polyglutamation, and increased tumor selectivity. In vitro, schedule-dependent synergy with both cisplatin and carboplatin has been demonstrated in human NSCLC lines [15, 16].

Carboplatin, a cisplatin analog, has demonstrated a reduced toxicity profile and a level of antitumor activity in NSCLC comparable to that of cisplatin [1, 8]. We performed a phase I study of edatrexate and carboplatin in advanced solid tumors. This study determined that the usual dose-limiting toxicity (DLT) of edatrexate given by a weekly schedule, mucositis, could be ameliorated with the simple maneuver of prophylactic ice-chip cryotherapy [5]. With the use of prophylactic cryotherapy, myelosuppression became the DLT. Though not an endpoint of the phase I study, tumor response was observed in 4 of 14 patients with NSCLC. Given the promising in vitro and in vivo results of this combination, a phase II trial of edatrexate and carboplatin was undertaken by the Southwest Oncology Group (SWOG 9207).

Patients and methods

Patient selection

Criteria for study entry consisted of histologically or cytologically demonstrated NSCLC not previously treated with chemotherapy. Patients were required to have measurable or assessable disease outside any previously irradiated field, a performance status of 0–2, a life expectancy > 8 weeks, a pretreatment white blood count ≥ 4000/l, platelet count $\geq 150\,000$/l, serum creatinine ≤ 1.5 mg%, and measured or calculated creatinine clearance ≥ 65 ml/min. A serum bilirubin and SGOT within 1.5 times institutional normal limits were required. Patients with known brain metastasis were excluded. All patients gave informed, written consent to participate in this multicenter SWOG study.

Treatment plan

Edatrexate was administered by intravenous infusion over 20–30 min weekly for 5 weeks (50% dose on day 8) and then every other week as previously described in a standardized schedule of administration [7]. Patients received prophylactic ice-chip cryotherapy for 5 min before, during, and for 15 min following administration of edatrexate, in an attempt to ameliorate mucositis.

Table 1 Patient characteristics

	No.	%
Patients	23	100
Age, (years)		
Median	59	
Range	39–72	
Sex		
Males	14	61
Females	9	39
Performance status		
0–1	21	91
2	2	9
Prior radiation or surgery		
Yes	11	48
No	12	52
Histology		
Squamous	5	22
Adenocarcinoma	8	35
Large cell	6	26
Unspecified	4	17

Carboplatin was administered at a dose of 350 mg/m^2 intravenously over at least 15 min on day 1 and repeated every 28 days. Carboplatin treatment was preceded by parenteral antiemetics and followed by an oral antiemetic regimen for 4 days to prevent delayed emesis.

Prior to each treatment day, a complete blood count (CBC), serum creatinine, and liver function tests were obtained, and interim other toxicities were assessed. Edatrexate was delayed on a weekly basis for a white blood count < 2500/l or platelet count $< 100\,000$/l, and reinstated at the next lower dose level. In addition, edatrexate was delayed for active mucositis, and dose reduced for mucositis of grade 3 or more or other severe nonhematologic toxicities. Treatment day criteria for carboplatin consisted of a white blood count of ≥ 3500/ml, platelet count $\geq 125\,000$/l, and calculated creatinine clearance ≥ 50 ml/l. Carboplatin was delayed for 1 week and reinstated at the next lower dose level for inadequate hematologic parameters or calculated creatinine clearance, or other toxicities of grade 3 or more. Therapy was continued for eight cycles (8 months) unless tumor progression was observed, toxicity criteria for removal of a patient from study were met, or a patient requested discontinuation.

Results

A total of 24 patients were accrued from 11 institutions, of whom 23 were eligible; there was insufficient documentation of eligibility in 1 patient. Patient characteristics are presented in Table 1. The principal toxicity observed (Table 2) was myelosuppression; grade 3–4 neutropenia was experienced by 8/23 patients. Two of the first six patients accrued died from neutropenic sepsis. Both patients had pleural effusions at the time of study entry. Subsequently, the study was amended to exclude patients with third space fluid collections. No

Table 2 Toxicity ($\geq$ grade 3)

	No. (%)
Hematologic	
Leukopenia	8 (35)
Anemia	2 (9)
Thrombocytopenia	6 (26)
Gastrointestinal	
Nausea/vomiting	4 (17)
Mucositis/stomatitis	3 (13)
Diarrhea	1 (4)
Anorexia	0 (0)
Constipation	1 (4)
Esophagitis	1 (4)
Renal	0 (0)
Infection/fever	5 (22)

Table 3 Response and survival

Response (no., %)	
Complete response	0 (0)
Partial response	3 (13)
Stable	4 (17)
Progression	7 (30)
Early death	3 (13)
Inadequate assessment[a]	6 (26)
Survival	
Median (months)	7
1 year (%)	30

[a]Assumed no response 26 July 1996

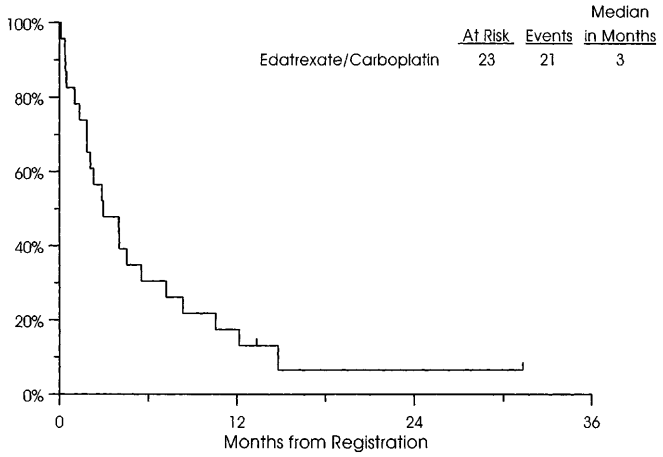

Fig. 1 Progression-free survival

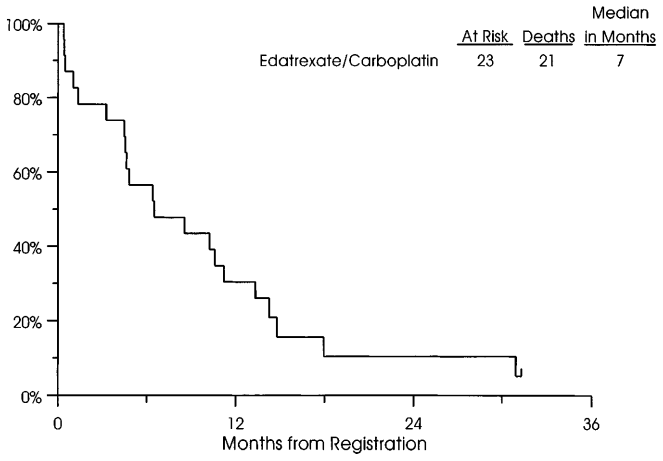

Fig. 2 Overall survival

further deaths attributable to therapy occurred. Oral mucositis was common, occurring in 14/23 patients, but was grade 3 in only 3/23 patients, confirming the efficacy of ice-chip cryotherapy [5]. No patient experienced grade 4 mucositis; a single patient had grade 4 diarrhea.

Partial response to therapy was observed in three patients (13%, 90% CI 1–26%; Table 3). Six patients did not have an adequate reassessment of disease status. By SWOG criteria, they are considered nonresponders. Median progression-free survival was 3 months, median survival time was 7 months, and 1 year survival was 30% (Figs. 1, 2)

Discussion

Cisplatin-based chemotherapy represents an advance in the treatment of NSCLC. Used in conjunction with radiation and/or surgery, survival benefit has been demonstrated in stage III disease, compared to local therapy alone [3]. In metastatic disease, modest gains have also been demonstrated with cisplatin chemotherapy, consisting of improved survival as well as palliation of symptoms [2, 4, 13, 18, 21]. However, cisplatin results in substantial nonhematologic toxicity in many patients, limiting its palliative benefit. Considerable effort has been directed toward development of cisplatin analogs with reduced toxicity and equal or superior efficacy. Carboplatin is an analog with an improved therapeutic index based on decreased nonhematologic toxicity and efficacy comparable to cisplatin in a number of different tumor types. In NSCLC, carboplatin response rates of 10–20% have been demonstrated in the cooperative group setting with median survival of approximately 6 months [1, 6, 8, 8, 14]. In a randomized trial, the combination of carboplatin plus etoposide was equivalent to cisplatin plus etoposide in terms of survival [10].

Edatrexate, a methotrexate analogue with enhanced activity, has also demonstrated activity in NSCLC. Response rates exceeding 15% have been demonstrated in several phase II studies [11, 19, 20]. Combinations with platinum have shown impressive activity both in vitro and in vivo. The principal toxicity of edatrexate given by a weekly schedule has been mucositis, with myelosuppression a secondary concern. Several strategies have been employed to overcome mucositis, including dose schedule modification, the use of leucovorin or folinic acid rescue, and ice-chip cryotherapy. Perez et al. have reported that delivering edatrexate on an every-other-week schedule allows a substantial increase in dose delivery [17]. Lee et al. have utilized leucovorin rescue to reduce mucositis, and have reported encouraging antitumor activity and tolerability of a combination of edatrexate, leucovorin, cyclophosphamide and cisplatin in NSCLC [12]. Our experience using prophylactic ice-chip cryotherapy to reduce the severity of mucositis has also been promising, allowing exploration of full-dose edatrexate in combination with other chemotherapeutic agents.

Unfortunately, the combination of edatrexate and carboplatin in this phase II study did not appear to improve outcome in stage IV NSCLC in comparison to previous regimens tested in SWOG. It is possible that the relatively low response rate observed in this study reflected the dosing of carboplatin on a milligram per meter squared basis, rather than area under the concentration × time curve (AUC), resulting in underdosing of carboplatin in some patients. Nevertheless, the median survival of patients treated with this regimen is comparable to that seen with other platinum-based regimens in the cooperative group setting. Unexpectedly severe myelotoxicity was experienced by two patients with underlying third space fluid collections, presumed to be the result of accumulation and prolonged elimination of edatrexate. This dose-schedule of edatrexate and carboplatin is not recommended for further evaluation in NSCLC.

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