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ORIGINAL ARTICLE

High-dose chemotherapy with peripheral blood progenitor cell support for patients with non-small cell lung cancer: the experience of the European Group for Bone Marrow Transplantation (EBMT) Solid Tumours Working Party

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We report the experience of the EBMT Solid Tumours Working Party (STWP) using high-dose chemotherapy (HDCT) with PBPC support in patients with non-small cell lung cancer (NSCLC). Between 1989 and 2004, 36 NSCLC patients (27 men and 9 women), median age 53.5 years (range: 24–62) were treated with 63 HDCT courses. A high-dose carboplatin-based regimen was used in 53% of the cases. Thirty-two patients had relapsed/metastatic disease, while four classified as stage IIIB received HDCT followed by radiotherapy. No treatment-related death occurred. Of 25 patients who were planned to receive multi-cycle HDCT, 4 cases (16%) interrupted the treatment early due to prolonged severe toxicities and 4 (16%) due to progressive disease. Of 36 evaluable patients, 3 (8%) achieved a complete remission and 13 (36%) had a partial remission at an overall response rate of 44%. Of these, one patient with stage IIIB and one with stage IV are alive disease free at 71+ and 149+ months, respectively. After a median follow-up of 48 months (range: 6–149), median survival was 7 months (range: 1–149). Despite one anecdotal case, HDCT did not show significant activity, but induced relevant morbidity in NSCLC patients.

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Introduction

The survival of patients with unresectable/metastatic non-small cell lung cancer (NSCLC) improved only minimally during the last 20 years, with a median survival ranging from 12 to 16 months.[1,2] The 5-year overall and disease-free survival rates for stage IIIB NSCLC patients are 15–20%, while for stage IV patients is 1–5% after conventional chemotherapeutic regimens.[1,2] Despite the substantial chemoresistance of NSCLC, several authors investigated the role of dose intensification with hematopoietic growth factor support to improve the prognosis of these patients.[3–6] Among lung tumors, dose-intensification strategies, including high-dose chemotherapy (HDCT) with PBPC, were mainly studied in small cell lung cancer (SCLC) with relevant activity emerging from phase II trials, but controversial efficacy resulted from randomized trials.[7–9] In the past years, several attempts have been made to improve the outcome of NSCLC patients, including the use of HDCT with PBPC in first-line setting, but only few case series have been reported in the literature.[10–13]

To better characterize this issue, we reviewed the database of the patients registered with the European Group for Blood and Marrow Transplantation (EBMT) for HDCT with PBPCs in patients with NSCLC and analyzed survival data.

Patients and methods

Data collection

From January 1989 to October 2004, a total of 69 patients with a diagnosis of NSCLC were registered with the EBMT. NSCLC were classified as adenocarcinoma, squamous-cell carcinoma, bronchiolo-alveolar carcinoma and undifferentiated epithelial lung cancer according to the World Health Organization (WHO) classification. We reviewed the registration details of these patients. The reporting physicians were contacted and asked to provide further information on histology, extent of disease, induction treatment, HDCT schedules and toxicities, further treatments and follow-up. For data collection, a standardized questionnaire was sent to each center. All patient data were obtained in an anonymous manner. Of 69

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Table 1 Patient characteristics

Characteristics	*No. of patients*
Total patients	36
Male/female	27/9
Median age, years (range)	53.5 (24–62)
Histology	
Adenocarcinoma	14
Squamous-cell carcinoma	11
Undifferentiated lung carcinoma	5
Low differentiated of adeno-squamous type	2
Other NSCLC histology	4
Staging	
IIIB	4
IV	32
Sites of disease	
Lung	21
Mediastinum	11
Liver	7
Bone	6
Cervical nodes	3
Central nervous system	2
Skin	2
Adrenal gland	2
Other	8
High-dose chemotherapy setting	
Up-front treatment[a]	27
After first-line induction chemotherapy	8
Third-line treatment	1

Abbreviation: NSCLC = non-small cell lung cancer.
[a]One/two courses of a mobilizing/induction chemotherapy given 2 months before initiation of high-dose chemotherapy.

registered cases, 47 (68%) questionnaires were returned. Of 47 initially received cases, 36 (77%) fulfilled eligibility criteria. The reasons for exclusion of 11 cases were as follows: another tumor diagnosis in 10 cases and double report of a case. Overall, we analyzed 36 cases of NSCLC treated with HDCT.

Patient characteristics

The details of the 36 patients with NSCLC treated with HDCT are listed in Table 1. The median age was 53.5 years (range: 24–62). Twenty-seven patients were men and 9 women. Thirty-two patients had relapsed/metastatic disease, while four were classified as stage IIIB according to the TNM classification.

Treatment

The induction/mobilizing regimens prior to HDCT consisted of high-dose epirubicin and cisplatin in 16 patients, other cisplatin-based regimens in 11 and other cyclophosphamide-based regimens in the remaining cases. The median number of induction treatment cycles was 1 (range: 1–5). Table 2 summarizes induction/mobilizing chemotherapy regimens and response. Twenty-five patients were treated with only one course of mobilizing chemotherapy that was planned to be followed by multiple courses of HDCT repeated every 3 weeks.

Table 2 Induction chemotherapy regimens and response

	No. of patients	*%*
Induction chemotherapy (no. of courses)		
High-dose epirubicin and cisplatin (1)	16	44
Other cisplatin-based regimens (1–4)	11	31
CY and etoposide (1)	5	14
CY and paclitaxel (5)	3	8
CY and ara-C (1)	1	3
Response		
Complete remission	0	0
Partial remission	11	31
Stable disease	6	17
Progressive disease	2	6
Not evaluated after single mobilizing course	17	47

Abbreviation: CY = cyclophosphamide.

In total, 63 courses of HDCT were administered. HDCT consisted of carboplatin area under the curve (AUC) = 10 and paclitaxel 400 mg/m^2 in 35 courses; cisplatin 165 mg/m^2, thiotepa 600 mg/m^2 alternated with cisplatin 165 mg/m^2 and carmustine 600 mg/m^2 in 12 courses; carboplatin AUC = 16 in 5 courses, cyclophosphamide 6 g/m^2, etoposide 750 mg/m^2 ± carmustine 800 mg/m^2 in 5 courses; and different high-dose melphalan-containing regimens in 6 courses. Sixteen patients underwent one course of HDCT, 13 received two courses, while in 7 cases, three courses were given. Patients were treated with one to three courses of HDCT based on HDCT approach in each center at the time when the treatment was administered. Overall, 60 courses were supported by PBPCs, and 3 by autologous BMT.

Statistical analysis

Descriptive statistics are presented as the median and range. Duration of follow-up and survival in this analysis were calculated based on the date of the first day of the induction chemotherapy until the date of last contact, if the patient was still alive, or until the date of death.

Results

Toxicity

Non-hematological toxicity data were assessable for all 63 HDCT courses delivered, while hematological toxicity data were complete in 52 courses (81%). No cases of treatment-related death occurred. In all patients, a median of 5.3×10^6 CD34+ cells/kg (range: 2.3–24.1) per course were re-infused. Grade 4 neutropenia and grade 4 thrombocytopenia occurred in a variable manner according to the HDCT regimen used with a complete hematopoietic recovery achieved in a median of 4 days (range: 0–15 days). The following non-hematological side effects were the most relevant: grade $\geqslant 3$ peripheral neurotoxicity was reported in 10 courses, grade $\geqslant 3$ asthenia in 5, grade $\geqslant 3$ stomatitis in 4, grade 2 renal toxicity in 1 and cerebellar syndrome in 1. Neither cardiac toxicity nor engraftment syndrome was observed.

Table 3 High-dose chemotherapy regimens and response

	No. of patients	*%*
High-dose chemotherapy regimen (no. of planned courses)		
Carboplatin and paclitaxel (3)	16	44
Cisplatin, thiotepa and carmustine (2)	6	17
Cyclophosphamide, etoposide ± BCNU (1)	5	14
Carboplatin (2)	3	8
Melphalan (1)	3	8
Other melphalan-based regimen	3	8
Response		
Complete remission	3	8
Partial remission	13	36
Stable disease	5	14
Progressive disease	15	42

Abbreviation: CY = cyclophosphamide.

High-dose chemotherapy response and survival

Of 36 evaluable patients, 3 (8%) achieved a complete remission (CR), and 13 (36%) had a partial remission (PR) for an overall response rate of 44%, while 5 (14%) had stable disease (SD) and 15 (42%) progressive disease (Table 3). In 4 cases with stage IIIB NSCLC, HDCT was followed by radiotherapy and patients obtained a CR in two cases and PR in two. Moreover, a patient with SD after HDCT received radical surgery with CR survived for 6 months. After a median follow-up of 48 months (range: 6–149), median survival was 7 months (range: 1–149). One patient with stage IIIB treated with multiple-cycle HDCT and one with stage IV undergone one HDCT course have been alive disease free at 71+ and 149+ months, respectively. In both cases, the response to induction therapy predicted for outcome to the HDCT regimen.

Discussion

The survival of NSCLC improved only minimally during the past years.[1,2] Despite the limited success of dose intensification with hematopoietic growth factors,[3–6] some investigators explored HDCT with hematopoietic support in patients with NSCLC in small series of patients, but the possible modest improvement in remission rates did not translate into a survival benefit and was associated with significant HDCT-related morbidity and mortality.[13] The Cancer and Leukemia Group B conducted a pilot study that consisted of two cycles of paclitaxel (250 mg/m^2) and carboplatin (AUC 18) supported by PBPCs in patients with locally advanced NSCLC.[12] Patients achieving a response to this induction treatment underwent surgical resection, thoracic radiation or both. This feasibility study examined clinical and pathologic responses to the toxic effects of this HDC regimen in locally advanced NSCLC. The authors stressed that regardless of the outcome of this study, large phase III trials will be needed to further define the role of HDC in NSCLC.[12] In a phase II study on HDCT in NSCLC, Fletscher *et al*.[14] enrolled 27 patients who received an HDCT course cycle consisting of etoposide 1500 mg/m^2, ifosfamide 12 000 mg/m^2, carboplatin 750 mg/m^2 and epirubicin 150 mg/m^2 followed by PBPCs after achieving a remission with two cycles of standard-dose induction chemotherapy with etoposide, ifosfamide, cisplatin and epirubicin. No advantage was observed with a 5-year survival of 0% in stage IV patients.[14,15] Overall, the literature on dose-intensified chemotherapy in NSCLC does not yet provide evidence of a benefit of HDCT.

To our knowledge, this EBMT experience represents the largest reported series on HDCT with PBPCs in NSCLC patients. Of 36 evaluable patients, 3 (8%) achieved a complete remission (CR), and 13 (36%) had a partial remission (PR) for an overall response rate of 44%. No toxic death occurred after induction/mobilizing regimens and after HDCT, but the lack of treatment-related mortality cannot be used as an indicator of the safety of this procedure because major comorbidities occurred, including severe peripheral neurotoxicity and stomatitis. After a median follow-up of 48 months (range: 6–149), median survival was 7 months (range: 1–149) with one patient with stage IV disease alive disease free at 149+ months. Despite this anecdotal case that received just one HDCT course, results of HDCT appeared inferior to those reported with conventional chemotherapeutic regimens with relevant side effects. No benefit of single vs multiple high-dose cycles in terms of response or response duration appeared, and the response to induction therapy predicted for outcome to the HDCT regimen. In addition, a potential positive selection bias could be considered, because HDCT has been administered to patients with good performance status and without comorbidity.[16] These results suggest that as with other diseases, sensitivity to standard doses of treatment is an important prognostic factor that can be used for predicting benefit from intensive therapy. If this approach were to be explored in future trials, then subsequent treatment with HDC should be limited to those patients achieving a significant response to induction therapy.

In conclusion, in the EBMT experience, early HDCT did not show significant activity in this patient population of young patients with good performance status. Despite this potentially favorable selection bias, median survival appeared poor. In view of these data, HDCT should not be considered for the next clinical trials in NSCLC patients, unless robust biological data will suggest specific subset of patient candidates for this treatment.

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Appendix

Institutions participating in this study

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