EUROPEAN JOURNAL OF CANCER 43 (2007) 885–890

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Response to melphalan in up-front investigational window therapy for patients with metastatic Ewing's family tumours

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ARTICLE INFO

Article history:
Received 16 July 2006
Accepted 23 September 2006
Available online 24 January 2007

Keywords:
Ewing's family tumours
Metastatic
Melphalan

ABSTRACT

The aim of the study was to determine the activity and toxicity of melphalan as a single agent given in up-front therapy for patients with newly-diagnosed Ewing's family tumours with bone/bone marrow metastases. Nineteen patients were enrolled from 2001 to 2004. The treatment consisted of up-front therapy with melphalan (two courses of 50 mg/m^2, 3 weeks apart). The overall rate of response to melphalan (complete response + partial response, according to the RECIST criteria) was 78%. Transient grade 3–4 neutropenia, thrombocytopenia and anaemia were recorded in 97%, 81% and 28% of melphalan courses, respectively. No other relevant toxicities were recorded.

Melphalan proved to be active in up-front treatment at non-myeloablative doses, and its toxicity was predictable and manageable. The schedule adopted did not interfere with any further intensive chemotherapy or myeloablative treatment in the majority of cases.

1. Introduction

The most important risk factor in Ewing's family tumours (EFT) is the presence of synchronous metastases at diagnosis. Nowadays, with the use of multidisciplinary treatment programmes, the 5-year overall survival probability exceeds 60% for patients with nonmetastatic EFT and is around 20% for patients with metastatic EFT.[1–4] A statistically significant difference in survival probability has been recognised in the latter, depending on the site of the spread. Metastatic disease in the bone or bone marrow carries a dismal prognosis, and long-term survivors with this presentation are rare, while cases in which the disease spreads to the lungs alone are associated with a survival probability that exceeds 30%.[5–10] The weak, but significant, improvement in clinical results obtained in the last 20 years for patients with metastatic

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.09.027

EFT in the lungs may be related to the use of more aggressive treatments. In fact, intensified chemotherapy has increased the percentage of clinical remissions, and the introduction of megatherapy could help to eradicate resistant clones.[11–13]

Melphalan is the drug most frequently used at myeloablative doses in the consolidation phase of investigational treatment programmes for EFT, but data on its activity at non-myeloablative doses in EFT are lacking.[8,11,13–17] Since the role of myeloablative treatment strategies in EFT has yet to be well defined and is still under investigation, any evidence of melphalan being active in these tumours would be helpful.[2]

The present study describes an up-front window therapy with melphalan in patients with newly-diagnosed EFT with bone/bone marrow metastases. The aims of the study were to evaluate the activity and acute toxicity of melphalan at non-myeloablative doses, in order to corroborate the rationale for continuing to use it in the consolidation phase of conditioning regimens followed by haemopoietic stem cell rescue, and establish whether it has a role in the treatment of EFT other than as a myeloablative therapy.

2. Patients and methods

In 2001, the Italian Sarcoma Group and the Associazione Italiana Ematologia Oncologia Pediatrica organised a study for patients with 'very high risk' EFT (VHR–EFT) at diagnosis. The term VHR–EFT refers to EFT with synchronous metastases involving the bone (more than one lesion) and/or bone marrow. Eligible patients were from 1 to 40 years of age, with a diagnosis of previously-untreated VHR–EFT. A biopsy-proven diagnosis of EFT was obtained in all patients. The initial evaluation included CT and/or MR of the site of the primary tumour, chest x-ray and CT, total-body 99-TC scan, bilateral bone marrow aspirates and biopsy, complete blood chemistry (including serum LDH level), echocardiography and ECG.

The up-front therapy consisted of two courses with melphalan, 50mg/sqm intravenously (i.v.) over 30 min, 3 weeks apart (Table 1). The second course of melphalan was started if the ANC was more than 1000/μL and platelets were more than 100,000/μL, and if there was no evidence of progressive disease on physical examination. The use of G-CSF after each course of melphalan was allowed, but discouraged during the up-front phase. The subsequent treatment programme (Table 1) started 3 weeks after completing the up-front therapy, or as soon as the ANC was 1000/μL and platelets were more than 100,000/μL, and it consisted of a total of eight intensive courses of chemotherapy. Leukapheresis for peripheral blood stem cell collection was planned during the intensive chemotherapy phase, in the absence of bone marrow infiltration as evaluated by bone marrow aspirate and biopsy. The leukapheresis was scheduled after cyclophosphamide + etoposide, followed as of day 4 by G-CSF 10 mcg/kg/d subcutaneously (s.c.). The minimum number of CD34+ cells to collect was 3×10^6/kg. When this threshold was not reached, a bone marrow harvest was planned to collect at least 1×10^8 mononucleated cells/kg. Local treatment with RT and/or surgery on the site of the primary tumour was programmed on an individual basis after four courses. Patients who achieved an objective response (complete or partial remission) after the eight-course chemotherapy received a consolidation treatment with melphalan 140 mg/sqm i.v. + busulphan 480mg/kg p.o. in divided doses daily for 4 days and autologous haemopoietic stem cell transplantation. A stopping rule on toxic death was established for the treatment programme. The treatment programme was approved by the local Ethical and Scientific Boards of all participating institutions, and written informed consent was obtained from patients or from legal tutors of patients <18 years old.

To evaluate the activity of up-front therapy with melphalan, the initial evaluation was repeated 3 weeks after the second course and before starting the subsequent treatment programme. Response was evaluated according to the RECIST criteria, with some modifications to adapt these criteria to EFT.[18,19] For the study purposes, the 'target lesions' were aribitrarily considered 1) the site of the primary tumour in all cases, evaluated with TC and/or MRI and 2) the metastatic measurable lesions >1 cm studied by TC and/or MRI, including also bone lesions selected basing on the 99-TC scan positivity, and were evaluated basing on three-dimensional measures. The 'non measurable-nontarget lesions' were considered 1) all the skeletal localisations assessed by 99-TC scan and not assessable for measures by TC and/or RMI, and 2) bone marrow infiltration, assessed by morphological evaluation of bilateral bone marrow and biopsy. The non

Table 1 – Treatment programme for patients with very high risk Ewing's family of tumours Week

0	3	6	9	12	15	18	21	24	27	30
Up-front L-PAM		VAI	CE ↓ PBSC collection by apheresis	VAI	CE (↓)	VAC	IE	VAC	IE	BuMel + ABMT
						RT/surgery→				

Up-front L-PAM: two courses of melphalan 50 mg/sqm i.v. over 30 min, 3 weeks apart; VAI: vincristine 1.5 mg/sqm (maximum dose 2 mg) on day 1, doxorubicin 45 mg/sqm daily on days 1–2, plus ifosfamide 3 g/sqm daily on days 1–2–3; CE: cyclophosphamide 4g/sqm on day 1, plus etoposide 200 mg/sqm/daily on days 2–3–4, plus G-CSF 10 μg/kg daily from day 6 to the day of collection of haemopoietic stem cells by apheresis; VAC: vincristine 1.5 mg/sqm (maximum dose 2 mg) plus cyclophosphamide 1.2 g/sqm on day 1 plus adriamycin 40 mg/sqm daily on days 1–2; IE: ifosfamide 1.8 g/sqm daily for 5 consecutive days plus etoposide 100 mg/sqm daily on days 1, 3, 5; BuMel+ABMT: busulphan 480 mg/sqm p.o. in divided doses daily for 4 consecutive days (on days -7,-6,-5,-4) plus melphalan 140 mg/sqm i.v. (on day -2) plus autologous haemopoietic stem cell rescue (day 0).
RT/surgery: local treatment at the site of the primary tumour on an individual basis from week 18.

measurable-non target lesions were considered as 'complete remission' if positive at onset and negative after the two courses with melphalan, 'stable disease' if remained positive, 'progressive disease' if negative at onset and positive after the two courses of melphalan. The overall response for all possible combinations of tumour responses in target and non target lesions with or without appearance of new lesions was assessed according to the RECIST criteria.[19] The tumour response to the treatment is described for each patient in Table 4.

The toxicity of each course of melphalan was recorded according to the National Cancer Institute's common toxicity criteria, version 2.0.[20] Any damage to myelopoiesis caused by the two courses of melphalan was evaluated considering possible delays between the up-front phase and the subsequent polychemotherapy phase, which was scheduled at 6 weeks. The mobilising capacity of the haemopoietic stem cells after the courses with cyclophosphamide-etoposide + G-CSF was also considered. If disease progression was documented at any time during the up-front phase, patients could proceed directly to the subsequent polychemotherapy phase. The study coordinator had to be notified of any grade 3 or 4 toxicity, with the exception of myelotoxicity, and the up-front therapy was to be withheld, pending an immediate discussion with the study coordinator.

The study was originally designed as a two-stage phase II study according to Simon.[21] A response rate of 20% or greater was targeted, with a 5% rejection error. A total of 17 patients entered the first stage. Should less than one favourable response (CR or PR) be observed in the first 14 patients, accrual was to stop and melphalan would not have been considered for further study. If at least one favourable response occurred in the first 14 patients, at least 30 patients would be collected. All patients were followed up for survival (time from starting treatment to death) and event-free survival (time from starting treatment to the first occurrence of progression, relapse after response, or death from any cause). Estimates of the time-to-event distributions were calculated using the Kaplan–Meier method, and confidence intervals were calculated for specific estimates of time-to-event distributions.[22]

3. Results

Between March 2001 and March 2004, 19 consecutive patients with a diagnosis of VHR–EFT at onset were enrolled in the study. The patients' characteristics are summarised in Table 2.

At diagnosis, the majority of patients had moderate to severe pain at the site of the primary tumour and/or at sites of metastases. LDH level was >1 n in 14 out of 19 patients. After the first course of melphalan, no relevant extra-haematological toxicity or progression of disease were recorded, so all patients completed the up-front therapy and are evaluable for response and the related toxicity.

Response to up-front therapy is shown in Table 3 and in Table 4. A partial remission was recorded in 15 patients, stable disease in two, and progressive disease in two. This result was considered sufficient to stop the the enrollment after 19 patients, and the melphalan therapy was considered active. A significant reduction in LDH was recorded in the 15 responders, about half of whom had a pathological value that returned within normal range. Pain also partially or completely disappeared in all these cases during the up-front phase, and step 2–3 analgesic therapy was discontinued within 2 to 6 weeks of starting the melphalan treatment.

Two patients had stable disease after the up-front therapy, but they had pathological LDH levels at onset that returned to normal after the up-front phase, and both had complete pain relief.

Disease progression was documented after the up-front phase in two patients, with an increase in the pain and worse general conditions in both cases.

There was no evidence to suggest that lack of response to the up-front therapy affected response to the subsequent therapy: among the four non-responders to melphalan, three showed a response to the subsequent polychemotherapy (data not shown).

All patients showed grade 3–4 haematological toxicity (Table 5), which – though transient – meant a median 3-day delay in the scheduled treatment after 14/38 courses. Notably, it was only in three patients that the interval between the start of phase II and the start of the subsequent phase was more than 1 week, and in one of them it was 4 weeks. The majority of delays were observed in patients with bone marrow invasion. Fever of unknown origin was recorded after 10/38 courses, without complications, and was always treated with antibiotics according to the institutional guidelines. No unusual toxicities were noted during the up-front therapy.

Sixteen of 19 patients had no bone marrow infiltration after phase II and were eligible for haemopoietic stem cell collection. In 12 of these (75%), an adequate number of CD34+cells was collected by apheresis alone, and in two by apheresis and bone marrow harvesting. The mean number of CD34+ cells collected by apheresis was 5×10^6/kg (range 2.3–12.5), with a mean number of two aphereses (range 1–5). The other two patients who were eligible for collection (both with bone marrow infiltration at diagnosis and in remission after the up-front phase) did not mobilise CD34+ cells and were scheduled for bone marrow harvesting, but suffered an early relapse and were withdrawn from the treatment programme. Only eight patients completed the polychemotherapy phase uneventfully and underwent the myeloablative phase as scheduled, and all of them had an adequate bone marrow graft (data not shown).

Though it was not among the aims of the present study, a survival analysis was performed. The 2-year survival and event-free survival for this cohort was 21 ± 10% and 13 ± 10%, respectively (Fig. 1). The median time to disease progression/relapse was 10 months (range 2–32), and only 8/19 patients (42%) completed the entire treatment programme as scheduled.

4. Discussion

In EFT, the use of high dose-intensity programmes probably enables a higher response rate to be obtained, but the use of myeloablative therapy as a 'consolidation' treatment modality has yet to be clarified.[1,2,8–10] Up to now, the only

Table 2 – Patients' characteristics

Total no. of patients	19
Males	10
Females	9
Median age, years (range)	17 (9–34)
Site of primary tumour	
Extremity	9
Pelvis	5
Rib	2
Vertebra	2
Clavicula	1
Metastatic sites	
Skeleton alone	3
Skeleton + other sites	16
LDH level	
Normal (<460 UI/L)	5
>1n	5
>2n	9
Pain requiring	Supportive care[a]
Step 3	13
Step 2	4
Step 1	1

a Analgesia according to WHO criteria: step 1 = mild to moderate pain requiring paracetamol ± coanalgesic (e.g. NSAID); step 2 = moderate pain requiring codeine ± coanalgesic; grade 3 = severe pain requiring morphine; one patient was asymptomatic at diagnosis.

Table 3 – Response after completion of up-front therapy with melphalan

	No. of patients	%
(RECIST criteria)[a]		
Complete response	0	–
Partial response	15	78.9
Stable disease	2	10.5
Progression of disease	2	10.5
Pain		
Complete regression	9	47.3
Partial regression[b]	6	31.5
Stable/worse	2	10.5
Not evaluable[c]	2	10.5
LDH level		
Remained within 1n	5	26.3
Normalisation of previous >1n	9	47.3
Reduction, but persistent >1n	2	10.5
No reduction/increment	1	5.2
Not evaluated	2	10.5

a See details in Table 4.
b Pain requiring paracetamol ± NSAID (all six required morphine before the up-front phase).
c Asymptomatic or requiring step 1 analgesia before the up-front phase.

randomised study attempting to address this issue is the ongoing EURO–Ewing trial.[2,12] In fact, the role of myeloablative therapy in EFT still has to be considered an investigational approach, which requires a careful evaluation of the activity of the drugs chosen for the conditioning regimen.[1,2,13] Nowadays, moreover, it is generally agreed to as much histotype-oriented therapies should be provided for sarcomas as possible, and examples of the application of this concept are the phase II studies in leiomyosarcoma and angiosarcoma.[23,24] Among the drugs used in myeloablative conditioning regimens for EFT, melphalan is the most widely used.[8–13] The use of melphalan in myeloablative regimens is based on data collected in phase II studies on other sarcomas (such as rhabdomyosarcoma), not on any formal prior evidence of its activity in EFT, with the exception of preliminary encouraging results at myeloablative doses.[16,17,25] That is why it would be useful to better define any activity of melphalan in EFT before continuing to use it. The present study attempted to assess the activity and toxicity of melphalan in up-front therapy for a cohort of patients with very high-risk EFT, also exploring whether melphalan could be used at non-myeloablative doses in EFT. The results of the present study indicate a response rate of EFT to melphalan at non-myeloablative doses that is comparable with, or even better than the response rate described with the six drugs used so far in the treatment in EFT, i.e. adriamycin, etoposide, cyclophosphamide, vincristine, dactinomycin, ifosfamide.[26] A partial response was recorded in 15 patients (78.9%), and that is why the enrollment was limited to 19 patients, and melphalan was considered active in this setting, even if we were aware that stopping the study earlier could decrease the power of the observed response rate and toxicity rate. The response to the up-front therapy was associated with a rapid improvement in the clinical conditions of these 15 patients, and with a decrease in the intensity of supportive care. In fact, most of them complained of severe pain requiring morphine, but after the up-front therapy only six of them required paracetamol or NSAID.

The toxicity recorded during the up-front therapy was limited to haematopoiesis, with grade 3–4 cytopenia in the majority of patients. Other toxicities were irrelevant and never more than grade 1. The haematological toxicity was transient and manageable in all cases, even in the patients who presented with pancytopenia due to bone marrow infiltration. In the majority of cases, these toxicities required no hospitalisation, and no relevant infections or haemorrhagic events were recorded.

Using melphalan (a well-known stem cell cytotoxic drug) for up-front window chemotherapy followed by prolonged and intensive chemotherapy may be questionable, but the choice was based on the multiple myeloma model, which has shown that stem cell harvesting is feasible even after six cycles of chemotherapy with melphalan, and patients can undergo myeloablative therapy and stem cell rescue.[27–29] The schedule adopted in the present study provides an early stem cell collection, and the results show that melphalan did not interfere with the yield of CD34+ cell apheresis in 14 of the 16 eligible patients. These results support the conviction that early mobilisation is needed before severe haemopoietic stem cell injury due to chemotherapy.[27] Two of the 11 patients with bone marrow metastases (both with severe bone marrow infiltration at diagnosis), however, failed to mobilise adequately. The presence of this 12.5% of poor mobilisers should prompt caution in applying intensive and

Table 4 – Details of the response after up-front therapy with melphalan

Pt#	Sex/age	Site of the primary tumour	Metastases	Response[a] after two courses with melphalan		Response for all possible combinations after two courses with melphalan			
				Primary tumour	Mestastases[b]	Target lesions	Non-target lesions	New lesions	Overall response
1	*f*/16	Tibia	S,L,BM	PR	SD,PR,CR	PR	SD	no	**PR**
2	*m*/16	Humerus	S	PR	SD	PR	SD	no	**PR**
3	*m*/14	Metatarsus	S	PR	SD	PR	SD	no	**PR**
4	*m*/17	Phalanx	S,L	SD	SD	SD	SD	no	**SD**
5	*m*/11	Pelvis	S, L,BM	PR	SD,PR,CR	PR	SD	no	**PR**
6	*m*/12	Vertebra	S,L,Li	PR	SD,PR,PR	PR	SD	no	**PR**
7	*m*/21	Pelvis	S,L,F,BM	PD	PD,PD,SD,n.e.	PD	PD	yes	**PD**
8	*m*/34	Calcaneus	S,L	PR	PR,PR	PR	PR	no	**PR**
9	*f*/9	Pelvis	S,BM	PD	PD,SD	PD	SD	yes	**PD**
10	*m*/16	Tibia	S,L,BM	PR	SD,PR,CR	PR	SD	no	**PR**
11	*f*/17	Clavicula	S,L,BM,CNS	PR	PR,PR,SD,PR	PR	SD	no	**PR**
12	*f*/19	Vertebra	S,L, soft tissues	PR	PR,PR,PR	PR	SD	no	**PR**
13	*f*/12	Femur	S,Li,CNS	PR	PR,PR,PR	PR	SD	no	**PR**
14	*f*/11	Fibula	S	PR	PR	PR	SD	no	**PR**
15	*f*/17	Ribs	S,L,F,BM	PR	PR,PR,PR,CR	PR	PR	no	**PR**
16	*m*/22	Ribs	S, L	PR	SD,PR	PR	SD	no	**PR**
17	*m*/10	Phalanx	S,L,BM	SD	SD,PR,CR	SD	SD	no	**SD**
18	*f*/14	Pelvis	S,L,Li,BM	PR	PR,PR,PR,CR	PR	CR	no	**PR**
19	*f*/13	Pelvis	S,L,Li,BM	PR	SD,PR,PR,CR	PR	SD	no	**PR**

S = skeleton; *L* = lungs; Li = liver; CNS = central nervous system; BM = bone marrow.
a Response according to the RECIST criteria, with modifications (see Section 2); CR = complete remission; PR = partial remission; SD = stable disease; PD = progressive disease; n.e.:not evaluated.
b In this column the response in each metastatic site is indicated.

Table 5 – Toxicities and transfusional supportive care during the up-front therapy

	1st course of melphalan (18 courses evaluable)	2nd course of melphalan (18 courses evaluable)
No. of courses with grade 3 neutropenia	5	5
No. of courses with grade 4 neutropenia	14	13
No. of courses with grade 3 thrombocytopenia	2	12
No. of courses with grade 4 thrombocytopenia	3	14
No. of courses with grade 3 anemia	5	6
No. of courses with grade 4 anemia	0	0
No. of febrile episodes	5	6
No. of admissions[a]	6	8
No. of pts transfused with PRC	9 (mean 2.5 units)	15 (mean 2 units)
No. of pts transfused with thrombocytes	11 (mean 1.5 units)	12 (mean 2.2 units)

a Admissions to hospital for surveillance/transfusional care or other supportive care.

myelotoxic treatment programmes, including melphalan or other agents which might cause bone marrow exhaustion, and confirms that collecting an adequate number of progenitor cells enables engraftment even after very intensive treatment regimens and myeloablative therapies.

In the present series of patients with very high-risk EFT, the use of up-front melphalan had no favourable impact on outcome and, despite the high rate of response to melphalan, disease progression was observed in the majority of patients, who died within 3 years of their diagnosis, as reported in the experience of other authors.[8] The use of high dose-intensity treatment programmes probably enables a higher response rate to be obtained, but this response rate unfortunately does not necessarily means a higher cure rate.[1,2,8,9,15,26] For patients with metastatic disease outside the lungs, investigational programmes need to be developed to attempt to modify the prognosis, which remains dismal.

In conclusion, the high response rate and mild toxicity profile of melphalan using the schedule adopted in this study suggests that this drug might be included, even at non-myeloablative doses, in the armamentarium of EFT therapy.

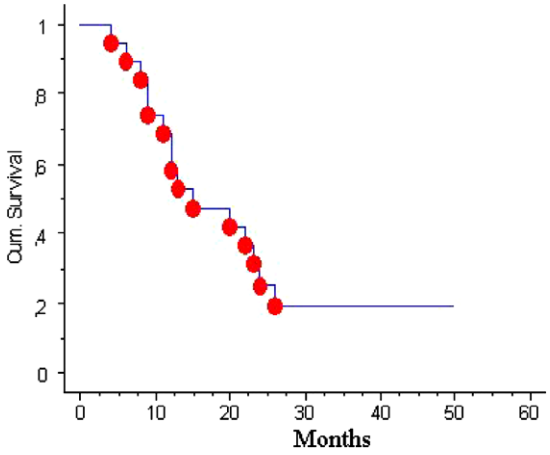

Fig. 1 – Kaplan–Meier curve for overall survival.

Conflict of interest statement

None declared.

Acknowledgement

This work was partially supported by Associazione Bianca Garavaglia, Busto Arsizio (VA), Italy.

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