JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Primary Disseminated Multifocal Ewing Sarcoma: Results of the Euro-EWING 99 Trial

Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Jeremy Whelan, Michael Paulussen, Odile Oberlin, Henk van den Berg, Uta Dirksen, Lars Hjorth, Jean Michon, Ian Lewis, Alan Craft, and Heribert Jürgens

From the St Anna Children's Hospital, Vienna, Austria; Children's Cancer Research Institute; Institut Gustave Roussy, Villejuif; University Paris-Sud, Le Kremlin-Bicêtre; Institut Curie, Paris, France; University College Hospital, London; Children's Day Hospital, St James University Hospital, Leeds; Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom; University Children's Hospital Basel, Switzerland; Emma Children's Hospital AMC, University of Amsterdam, Amsterdam, the Netherlands; University Children's Hospital, Münster, Germany; and Lund University Hospital, Lund, Sweden.

Submitted March 23, 2009; accepted April 8, 2010; published online ahead of print at www.jco.org on June 14, 2010.

Supported in part by the United Kingdom Department of Health's National Institutes of Health Research Biomedical Research Centers funding scheme (a proportion of funding provided to hospitals in the United Kingdom where this work was in part undertaken). The German Society of Pediatric Hematology and Oncology Ewing Sarcoma Working Group is funded by Deutsche Krebshilfe.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Ruth Ladenstein, MD, St Anna Children's Hospital, S²IRP–CCRI Studies and Statistics on Integrated Research and Projects, Children's Cancer Research Institute, Kinderspitalgasse 6, 1090 Vienna, Austria; e-mail: ruth.ladenstein@ccri.at.

0732-183X/10/2899-1/$20.00

DOI: 10.1200/JCO.2009.22.9864

ABSTRACT

Purpose
To improve the poor prognosis of patients with primary disseminated multifocal Ewing sarcomas (PDMES) with a dose-intense treatment concept.

Patients and Methods
From 1999 to 2005, 281 patients with PDMES were enrolled onto the Euro-EWING 99 R3 study. Median age was 16.2 years (range, 0.4 to 49 years). Recommended treatment consisted of six cycles of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE), one cycle of vincristine, dactinomycin, and ifosfamide (VAI), local treatment (surgery and/or radiotherapy), and high-dose busulfan-melphalan followed by autologous stem-cell transplantation (HDT/SCT).

Results
After a median follow-up of 3.8 years, event-free survival (EFS) and overall survival (OS) at 3 years for all 281 patients were 27% ± 3% and 34% ± 4% respectively. Six VIDE cycles were completed by 250 patients (89%); 169 patients (60%) received HDT/SCT. The estimated 3-year EFS from the start of HDT/SCT was 45% for 46 children younger than 14 years. Cox regression analyses demonstrated increased risk at diagnosis for patients older than 14 years (hazard ratio [HR] = 1.6), a primary tumor volume more than 200 mL (HR = 1.8), more than one bone metastatic site (HR = 2.0), bone marrow metastases (HR = 1.6), and additional lung metastases (HR = 1.5). An up-front risk score based on these HR factors identified three groups with EFS rates of 50% for score ≤ 3 (82 patients), 25% for score more than 3 to less than 5 (102 patients), and 10% for score ≥ 5 (70 patients; $P < .0001$).

Conclusion
PDMES patients may survive with intensive multimodal therapy. Age, tumor volume, and extent of metastatic spread are relevant risk factors. A score based on these factors may facilitate risk-adapted treatment approaches.

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INTRODUCTION

Presence of metastases is the most prominent adverse prognostic factor in Ewing sarcoma (ES).[1-8] Metastases at diagnosis are detected in 15% to 33% of patients,[2,3,5,9-11] with survival rates from 9% to 41%[3,9,10,12-14] as compared with the survival expectancy of patients with localized disease of approximately 70%.[15-17] Patients with primary pulmonary metastases fare better than patients with primary bone and/or bone marrow (BM) involvement.[13,18] Reports on outcome in patients with metastatic disease may be confounded by the varying number of patients included with lung metastases as the sole metastatic site. Patients with lung metastases only were shown to have a better prognosis, with event-free survival (EFS) ranging from 29% to 52%, especially when bilateral lung irradiation or myeloablative high-dose therapy (HDT) were added.[5,13,19-21] In contrast, patients with bone/BM metastases had an EFS of 19% and of only 8% in the presence of combined lung and bone/BM metastases ($P < .0001$).[2,3,5,9-11,21] Various front-line strategies[22-25] have been explored in ES as well as HDT with or without total-body irradiation[6,26] followed by autologous or allogeneic stem-cell transplantation (SCT).[2,10,27-29] Some reports have shown improved outcome with impressive remission rates,[30-32] whereas others did not.[28] An analysis of the European Group for Blood and Marrow Transplantation registry data showed a better outcome for patients with ES who received a busulfan-containing regimen as compared with other HDT regimens.[30,31,33] Thus the busulfan-melphalan (BU-MEL) HDT strategy was the recommended treatment for patients with primary

disseminated multifocal ES (PDMES) completing vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) induction therapy[23] in the European Ewing Tumor Initiative of National Groups (Euro-EWING 99, EE99) protocol.

PATIENTS AND METHODS

Eligibility Criteria

Patients with newly diagnosed ES, including peripheral neuroectodermal tumors, with primary disseminated disease and age younger than 50 years were eligible. Patients with isolated lung metastases were not part of this analysis. The diagnosis of ES was confirmed by pathologic and immunohistochemical features, including CD99. Molecular testing for EWS Fli-1 fusion transcript was recommended.

The protocol was reviewed and approved by the appropriate institutional review boards, ethical committees, and legal authorities. Informed consent was obtained from all patients or legal guardians according to the Declaration of Helsinki and national guidelines.

Pretreatment Evaluations

Staging procedures consisted of conventional radiographs and computed tomography (CT), magnetic resonance imaging (MRI), and whole-body technetium bone scan. BM was assessed by multiple aspirates and biopsies distant from the primary tumor or known metastatic sites. Confirmatory radiographs and MRI for suspected bone or soft tissue metastases were recommended. Tumor volume was based on MRI or CT scan imaging with either computed volumetry or by estimation of tumor volume by the appropriate formula: If exact measurements were unavailable, volume was categorized as less than or $\geq$ 200 mL.

Chemotherapy

Induction chemotherapy consisted of six cycles of VIDE and one cycle of vincristine, dactinomycin, and ifosfamide (VAI) as previously published.[23]

Local Therapy

Resection of primary and metastatic tumor sites was recommended after VIDE cycle 6, unless this would cause delay of further systemic treatment beyond 6 weeks. In such cases, local therapy was to be postponed until 6 to 8 weeks after the completion of HDT and stable engraftment.

Patients were, where feasible, to receive radiotherapy to bulky residual primary tumor and metastases. Radiotherapy of central axial sites had to be delayed until after BU-MEL HDT. Patients with early radiotherapy to central sites and patients in need of radiotherapy to areas including parts of the spinal cord or brain were ineligible for busulfan-containing HDT for reasons of anticipated toxicity. Alternative approaches, for example, double melphalan-etoposide (ME-ME) HDT,[34] were suggested.

Table 1. Patient Characteristics and Univariate Analysis of Clinical Features for EFS and OS

Characteristic	Patients		3-Year OS				3-Year EFS			
	No.	%	Deaths	Mean	SD	*P*	No. of Events	Mean	SD	*P*
Sex										
Male	158	57	107	0.33	0.04	.811	117	0.26	0.04	.837
Female	121	43	81	0.35	0.04		89	0.27	0.04	
Age, years										
≤ 14	99	35	54	0.46	0.05	< .001	61	0.40	0.05	< .001
> 14	182	65	134	0.27	0.03		145	0.19	0.03	
Primary tumor site										
Extremity	84	31	51	0.39	0.06	.098	56	0.32	0.05	.060
Chest/spine/HN	65	24	43	0.39	0.06		47	0.27	0.06	
Abdomen/pelvis	124	45	89	0.28	0.04		97	0.24	0.04	
Primary tumor volume, mL										
< 200	93	35	45	0.55	0.05	< .001	56	0.44	0.05	< .001
≥ 200	171	65	129	0.23	0.03		134	0.19	0.03	
Sites of metastases										
BM (plus lungs)	26 (7)	10	12	0.55	0.10	.001	13	0.52	0.10	< .001
Bone (plus lungs)	121 (66)	45	77	0.37	0.05		85	0.31	0.04	
Bone plus BM (plus lungs)	97 (36)	36	78	0.21	0.04		82	0.14	0.04	
Other (plus lungs)	27 (14)	10	13	0.55	0.10		16	0.36	0.10	
No. of bone lesions										
None	53	19	26	0.53	0.07	< .001	30	0.43	0.07	< .001
Single lesion	40	14	23	0.43	0.08		24	0.40	0.08	
2-5 lesions	81	30	60	0.30	0.05		65	0.23	0.05	
> 5 lesions	100	36	77	0.24	0.04		85	0.16	0.04	
Additional lung metastases										
Not present	150	54	91	0.43	0.04	< .001	101	0.34	0.04	< .001
Present	129	46	97	0.22	0.04		105	0.17	0.03	
Involvement										
Osseous	242	88	159	0.35	0.03	.058	176	0.28	0.03	.189
Extraosseous	34	12	26	0.28	0.08		27	0.18	0.07	
Risk score										
≤ 3	82	32	36	0.62	0.05	< .001	45	0.50	0.06	< .001
> 3-< 5	102	40	69	0.28	0.05		73	0.25	0.04	
≥ 5	70	28	62	0.15	0.04		64	0.10	0.04	

NOTE. All 281 registered patients were kept within the prospective cohort for analysis. Patients with incomplete data sets on some items were not excluded.
Abbreviations: EFS, event-free survival; OS, overall survival; SD, standard deviation; BM, bone marrow.

Stem Cell Collection

Autologous peripheral-blood stem cells collected after granulocyte colony-stimulating factor stimulation were used as the preferred graft source. The recommended cell dose per procedure was $\geq 3 \times 10^6$ CD34cells/kg of body weight. In case of persistent BM disease, collection was delayed until after clearance of the BM.

BU-MEL High-Dose Chemotherapy

To proceed to HDT, patients had to have responding disease. The proposed HDT consisted of oral busulfan 150 mg/m^2/d on days -6, -5, -4, and -3 and melphalan 140 mg/m^2 on day -2, followed by stem cell rescue on day 0.

Statistical Analyses

All registered patients were analyzed, excluding patients for whom the diagnosis of ES was changed after expert pathologist review (n = 4). Overall survival (OS), median OS, and EFS were estimated from the time of diagnosis by the Kaplan-Meier method. Disease progression, new metastases, second malignancies, or death from any cause were considered as events for EFS analyses; otherwise, patients were censored at the date of last contact.

Factors considered for univariate analyses by log-rank tests[35] were sex, age, primary tumor site and volume, sites of metastases, number of bone lesions, lung metastasis, and extra-osseous involvement. These factors were included in the multivariate Cox regression,[36] regardless of their significance in univariate regression. Validation of model calibrations (ie, the model's ability to make unbiased estimates of outcome) used the bootstrap method.[37] An additive scoring based on the rounded log-hazard ratios was created.[38]

For the comparison of HDT-related prognostic factors and HDT regimens, EFS and OS were calculated from initiation of HDT. To adjust for the waiting time bias to receive either local treatments or HDT, both were included in the Cox model as time-dependent covariates.[39] Ignoring the time-dependent nature of both would yield a biased effect on size estimation in favor of local treatments as well as HDT.

RESULTS

From September 1999 to December 2005, 281 patients with newly diagnosed PDMES were enrolled onto the protocol via the Children's Cancer and Leukemia Group, the German Society of Pediatric Oncology and Hematology, or the Société Francaise des Cancers de l'Enfant. The Euro-EWING 99 committee agreed to the stop enrollment to this group and to release the data. The cutoff date of this analysis was February 2008. Median age was 16.2 years (range, 0.4 to 49 years). Patient characteristics are listed in Table 1.

Patient Flow Through Treatment

All six VIDE cycles were completed in 250 (89%) of 281 patients. Reasons to omit or change strategy are summarized in Figure 1.

High-Dose Chemotherapy

Of 281 patients, 169 (60%) received HDT/SCT. Of note, 112 patients did not receive HDT because of early progression, physician and patient choice, and collection failure in four patients. The median time from diagnosis to start of HDT was 188 days (range, 137 to 301 days). Before HDT, the response status of these 169 patients was classified as complete remission (CR), partial remission (PR), stable disease, and progressive disease in 24, 91, 27, and three patients, respectively (response was not evaluable or not specified in 24 patients).

BU-MEL was used for 136 (80%) of 169 patients. Double ME-ME was given to 13 patients (8%), whereas other HDT regimens were chosen by local investigators in 20 patients (12%).

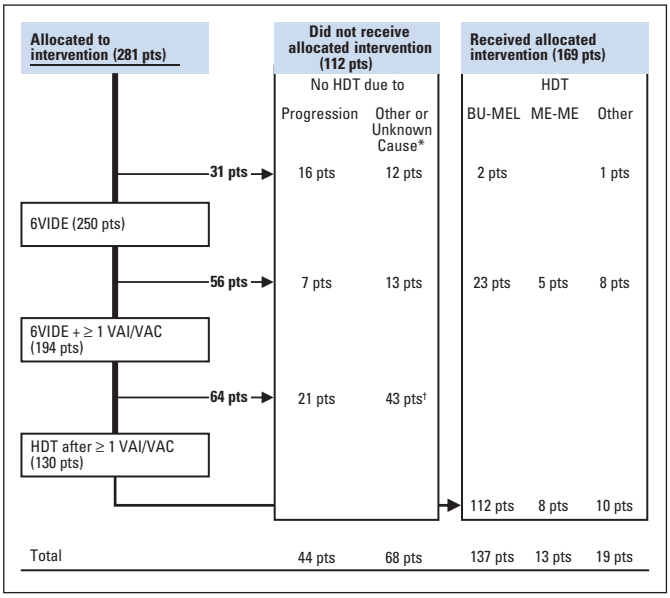

Fig 1. Flow chart of patients through treatment: (*) Local physicians and/or patients choices; (†) patients continued on conventional chemotherapy because of failure of stem cell collection in four patients or based on local physicians and/or patients choices. HDT, high-dose treatment; pts, patients; BU-MEL, busulfan and melphalan; ME-ME, double course of melphalan plus etoposide; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide; VAI, vincristine, dactinomycin, ifosfamide; VAC, vincristine, dactinomycin, and cyclophosphamide.

The median recovery times after HDT were 11 days to reach 10^3/L WBCs, 12 days to reach 500/L absolute nucleated cells, 12 days for platelets more than 20×10^3/L, and 19 days for platelets more than 50×10^3/L. Median recovery times were similar for all HDT regimens.

Local Treatment to Primary Tumor

A total of 203 patients (77%) received local treatments: 71 patients received surgery only, 90 patients received irradiation only, 42 patients received a combination of both, and 62 patients had no local treatment; 16 patients had no information on local therapy. Surgery was performed in 81 patients at different times: at diagnosis in six patients, before HDT in 39 patients, after HDT in 25 patients, and at an unspecified time point in 11 patients.

Among the 169 patients treated with HDT, 148 patients (88%) received local treatment: 53 patients had surgery, 69 patients had irradiation, 26 patients had a combination of both, and 21 patients had no local treatment. Radiotherapy was administered to 95 patients: after HDT in 79 patients and before HDT in eight patients; in eight patients, the timing was not specified.

In contrast, only 54% of patients not receiving HDT had some sort of local treatment. Early progressions were the main reason, but tumor load and local tumor extension also influenced local decisions to omit local treatment.

Induction Toxicity

Toxicities observed in the PDMES population were comparable to previously reported data on VIDE toxicities.[23] One patient died during VIDE chemotherapy as a result of severe sepsis and cardiac decompensation.

HDT Toxicity

As expected, HDT regimens caused profound grade 4 aplasia in 93%, but with acceptable grade 3 and 4 infection rates. Stomatitis dominated the gastrointestinal toxicities. Parenteral analgesia was required in 93 (77%) of 121 patients receiving BU-MEL and was reported in 62% (16 of 26 patients) with other regimens. Parenteral nutrition was received by 70% (85 of 121 patients) after BU-MEL and in 20 of 27 patients (74%) after other regimens. Veno-occlusive disease (VOD) was reported for 22 (19.5%) of 113 patients after BU-MEL and in three (12%) of 26 patients after other regimens. Four of the 22 VOD episodes after BU-MEL were grade 1 (18%), 13 grade 2 (59%), and 5 grade 3 (23%). Pulmonary toxicity was reported in 2 patients (1.6%) after BU-MEL.

Transplant-Associated Mortality

Three patients died within the first 100 days after BU-MEL HDT, one as a result of acute respiratory distress syndrome and two as a result of severe VOD and septicemia. A further three patients died due to digestive tract late radiation toxicity 1 to 1.5 years after BU-MEL HDT.

Another patient died as a result of postallograft toxicity; allograft was performed as clinician choice.

No second malignancies were recorded at the date of analysis.

Outcome

The 3-year EFS rate in the 281 patients was 27% (standard deviation [SD], 3%), and the OS rate 34% (SD, 4%), with a median follow-up of 3.9 years after diagnosis and 84% of survivors with follow-up greater than 2 years. Median survival time was 1.6 years for all patients. Of 44 patients with early disease progression before HDT, 43 died. Their median survival time was 0.87 months (range, 0.16 months to 2 years). One patient experiencing disease progression received other HDT after six VIDE cycles and died 17 months after diagnosis.

At analysis, 93 of 281 patients were still alive, of whom 64 patients had received HDT. However, 82% of patients without HDT died after a median time of 1 year. Beyond year 2, a further seven deaths occurred.

Prognostic Factors

Significant unfavorable factors at diagnosis found in univariate analysis are shown in Table 1 and Figure 2. The multivariable risk factor analysis is summarized in Table 2.

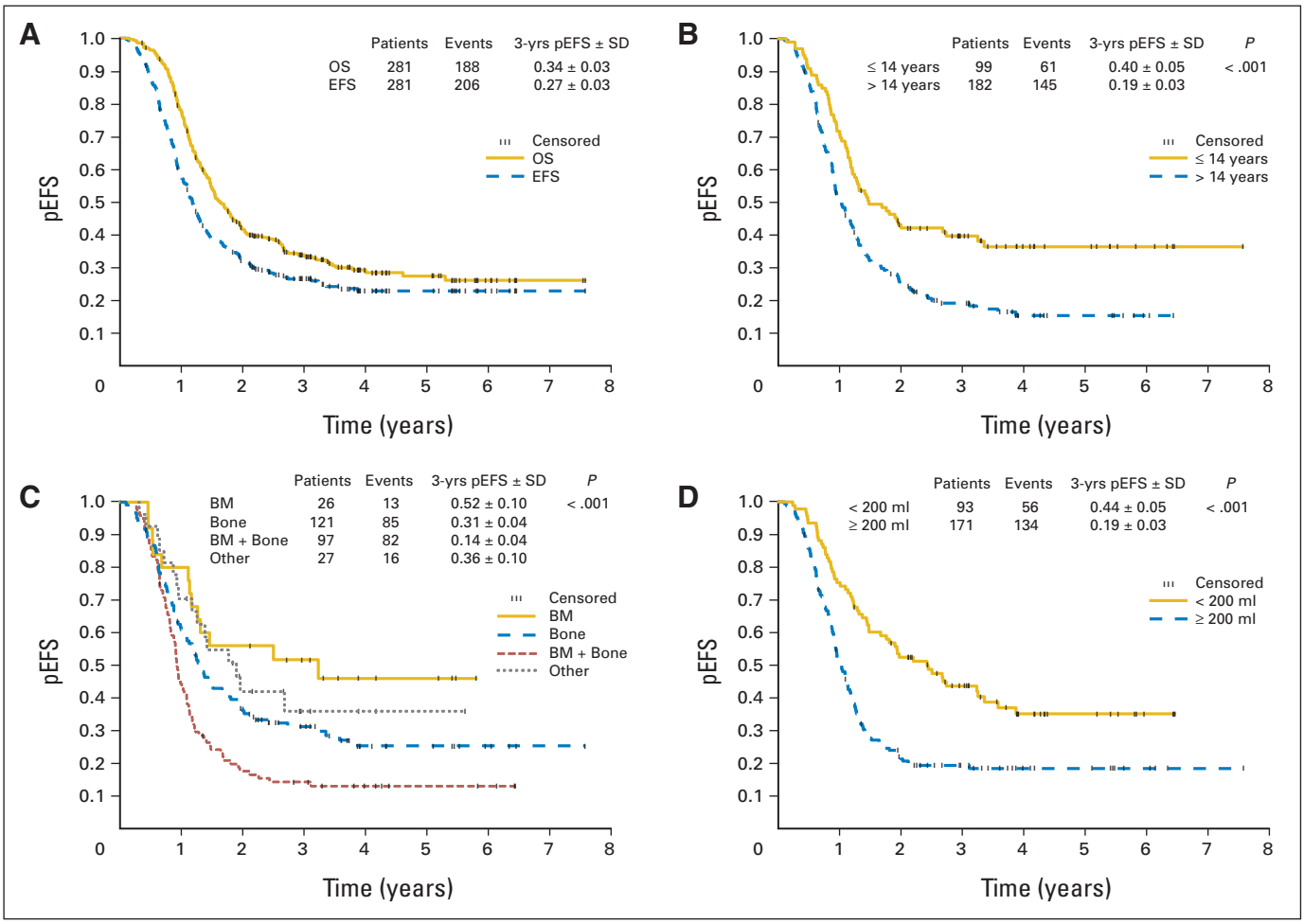

Fig 2. Outcome according to univariate parameters at diagnosis in the unselected patients with primary disseminated multifocal Ewing sarcomas. OS, overall survival; EFS, event-free survival; BM, bone marrow; pEFS, probability of event-free survival.

Table 2. Multivariate Analyses of EFS Performed With the Cox Proportional Hazards Model Including 253 Patients (181 events, full cases only)

Prognostic Factor	*P*	Hazard Ratio	95% CI	Score Points
Age, years				
≤ 14		1		0
> 14	.003	1.7	1.2 to 2.4	1
Bone metastases (*v* none)	.026			
None		1		0
Single lesion	.124	1.6	0.9 to 2.8	1
2-5 lesions	.005	2.0	1.2 to 3.3	1.5
> 5 lesions	.005	2.0	1.2 to 3.1	1.5
BM metastases (*v* none)				
None		1		0
BM metastases	.004	1.6	1.2 to 2.2	1
Primary tumor site (*v* extremities)	.323			
Extremities		1		—
Chest/spine/HN	.183	0.7	0.5 to 1.2	—
Abdomen/pelvis	.831	1.0	0.7 to 1.4	—
Osseous *v* extraosseous ET				—
Osseous		1		—
Extraosseous	.706	1.2	0.7 to 1.9	—
Primary tumor volume, mL				
< 200 mL		1		0
≥ 200 mL	.001	1.8	1.3 to 2.5	1.5
Lung metastases (*v* none)				
None		1		0
Lung metastases	.006	1.5	1.1 to 2.1	1

Abbreviations: EFS, event-free survival; BM, bone marrow; HN, head and neck; ET, Ewing tumors.

Outcome after HDT (Appendix Fig A1, online only) with respect to the remission status resulted in 3-year EFS rates of patients in CR of 57% (SD, 10%), 32% (SD, 5%) for patients in PR, and 24% (SD, 7%) for patients with stable or progressive disease ($P = .017$). The type of HDT had no significant influence on EFS, with 3-year EFS rates of 32% (SD, 4%) for 127 patients receiving BU-MEL, 0% for 13 patients receiving ME-ME, and 20% (SD, 10%) for 15 patients receiving other HDT regimens. Forty-six children younger than 14 years with PDMES had a promising 3-year EFS of 45%.

Development of a Prognostic Scoring Model at Diagnosis

The individual risks were brought into a scoring model to predict outcome at diagnosis.

The relationship between the number of events and the number of potential predictors was considered favorable for the reliability of the fitted model. The model calibration was validated, showing the model's ability to make unbiased estimates of outcome. The parameter estimates in Cox regression are log-hazard ratios and are on an additive scale. For each patient, the sum of the parameter estimates for risk factors being found reflect the risk of a patient to experience an event. Taking the quartiles of these risk scores, four approximately equal-sized risk groups could be defined with the following 3-year EFS rates: 53% for a score less than 1.85, 34% for a score range of 1.85 to 2.30, 20% for the score range of 2.31 to 2.75, and 9% for scores more than 2.75 (Fig 3A).

As a next step, an additive score was constructed for easier clinical use. The values of the score points are based on log-hazard ratios. Among the significant risk factors, the factor with the smallest hazard ratio (HR) has been taken as basis and assigned one point. The remaining factors are assigned according to their relative impact. For simplification and to improve the feasibility of the application of the score, scoring points are rounded.

Hence one score point each was attributed to the following risk factors: age older than 14 years, BM metastasis, one bone lesion, and additional presence of lung metastases, whereas 1.5 points were attributed to the risk factors of primary tumor volume ≥ 200 mL and more than one bone lesion (Table 2). This risk score allowed allocation of patients with PDMES at diagnosis to three risk groups with significantly different outcome ($P < .0001$): group 1 (score ≤ 3; 82 patients) with an EFS of 50%, group 2 (score > 3 to < 5; 102 patients) with an EFS of 25%, and group 3 (score ≥ 5; 70 patients) with an EFS of 10% (Fig 3B). The distribution of the various risk factors within the three balanced score groups are detailed in Table 3.

Although there was a significant difference in outcome between countries, as the risk distribution differed by country, adjusting for country did not influence the impact of the risk factors on EFS.

To value the impact of local therapies as well as HDT on EFS, the waiting time bias was considered, as patients need to survive long enough to receive local therapy or HDT. To highlight inherent tumor-associated risks at diagnosis, we demonstrated that patients without surgery had a higher median risk score of 4, whereas those with surgery of the primary tumor had a median risk score of 3 ($P < .001$). The median score for patients with and without HDT is 3 and 3.5, respectively ($P = .025$). The adjusted model shows that once patients became eligible for surgery (HR = 0.7; $P = .045$) and HDT (HR = 0.51; $P < .001$), both contribute significantly to improved EFS rates. This was not the case for radiotherapy, taking its time-dependant nature into account.

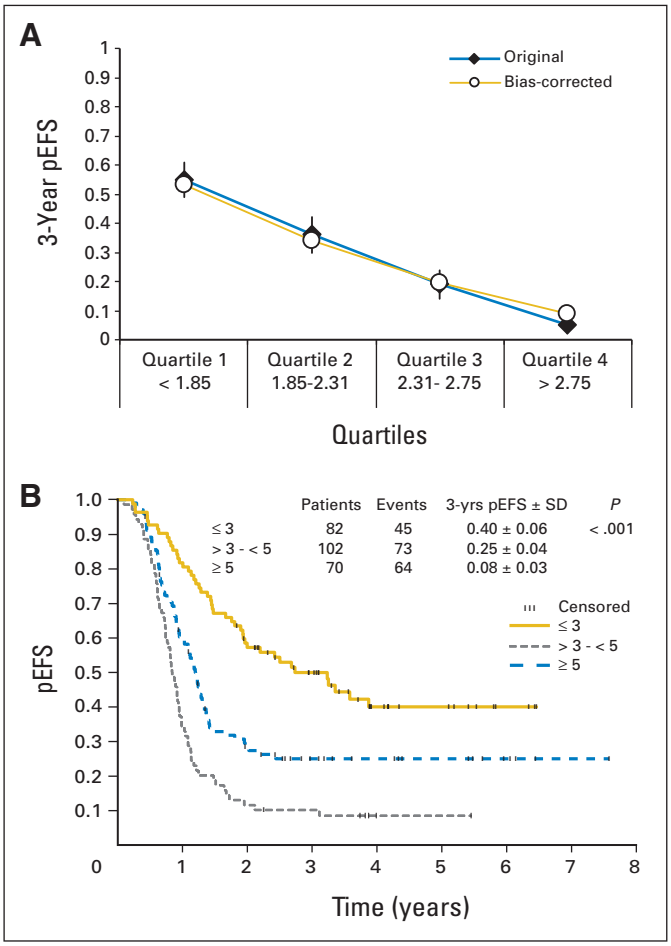

Fig 3. Risk model validation and outcome according to risk groups. (A) Original model: 3-years probability of event-free survival (pEFS) using the same data to develop the model and to assess its performance; bias-corrected: adjusted for optimism by a bootstrap technique to penalize for possible overfitting. (B) pEFS based on the respective score process of the whole unselected patient cohort recruited on study.

Hence it is not possible to compare outcome for patients receiving HDT and those who did not because of the bias introduced by early progression, as well as higher baseline scores and a lower frequency of application of local control therapy in those patients not receiving HDT.

Confirmation of Score in an Independent Data Set

For comparison, 44 patients with PDMES from a previously published French study[21] were analyzed to test the independent prognostic significance of the proposed score. Their 3-year EFS rates were as follows: score group 1 (18 patients), 50% (95% CI, 29% to 71%); score group 2 (15 patients), 20% (95% CI, 2% to 37%), and score group 3 (11 patients), 9% (95% CI, 2% to 37%; $P = .04$; Oberlin, personal communication, January 2008).

DISCUSSION

This Euro-EWING 99 study report on 281 unselected, prospectively treated patients represents the largest group of patients with ES with primary disseminated multifocal disease reported so far and shows a 3-year EFS of 27% and an OS of 34%. A number of reports have confirmed the unfavorable prognosis of patients with primary metastatic ES.[3,13,14,21,33,34] In the early Cooperative Ewing Sarcoma studies using conventional chemotherapy in the majority of the patients, no patients with bone metastases survived disease-free.[34] The Société Francaise des Cancers de l'Enfant using BU-MEL HDT/SCT achieved a 24% EFS for patients with PDMES.[21] Other reports of more favorable outcome after HDT suffer in part small numbers but underline the importance of pre-HDT response.[1,2,10,12,27,29-32,40] In our study, the EFS of 57% and 25% for patients in CR and PR after HDT compares well with that of previous reports.

Small PDMES patient groups achieved promising response rates with melphalan-based HDT regimens.[1,2,10,27,30,31] Several studies with various HDT included total-body irradiation or total-marrow irradiation but still resulted in moderate outcomes.[10,27,41]

We further observed that prognosis differed with the type and extent of metastatic spread. The small group of patients[26] with BM involvement as the only metastatic spread had a 52% EFS, in contrast with other reports showing that BM involvement by itself was a particularly unfavorable prognostic factor.[21,28,42,43] In our series, we were able to show an increasing risk related to the number of skeletal metastatic lesions, with more than five at diagnosis clearly resulting in an EFS of only 16%. The negative influence of the additional presence of lung metastases in PDMES confirms other meta-analyses.[3,14,20] In a small group of 16 patients with metastatic spread limited to sites outside the skeleton and BM, we found a rather favorable EFS rate of 36%.

The primary tumor volume is a strong independent prognostic factor, even in patients with PDMES, and is more important than the site of the primary tumor. A trend toward worse outcome for central tumors was seen, which may reflect problems in local control.

Cox regression analyses confirmed the independent prognostic importance of the presence and number of bone lesions, primary tumor volume greater than 200 mL, age older than 14 years, and additional pulmonary metastases, as well as BM involvement.

These prognostic factors were used to develop a prognostic score to discriminate at diagnosis subgroups with different outcome to develop risk-tailored treatment strategies. Retrospective application of this risk score to a historical group of French patients has confirmed the validity.

Many factors can impact the feasibility, modalities, and timing of proposed treatments. The risk score highlights that the local decision-making processes for local therapy and HDT were influenced by inherent disease risks apart from possible individual aspects. More importantly, it provides a tool at diagnosis to identify very high-risk patients with PDMES for experimental treatments early, whereas patients with PDMES having a low-risk score can expect a more favorable prognosis, with an EFS up to 50%.

A comparison of outcome of patients with and without HDT was not performed because this study was clearly not performed in a planned randomized setting. It is noteworthy that reasons to refrain from HDT as well as from local control measures[44] were related to particularly high-risk disease features at diagnosis and unsatisfactory disease control during induction therapy.

Further improvements of treatment strategies in this highest risk group of patients with PDMES are urgently needed. This may include targeted therapies, which are currently being explored in early clinical trials,[45] as well as refinement of HDT concepts allowing for a better local control rate.

Table 3. Distribution of Risk Factors According to Multivariate Analysis Within Risk Groups

Risk Score	Age > 14 Years (score point 1)	Volume > 200 mL (score point 1.5)	1 Bone Lesion (score point 1)	> 1 Bone Lesion (score point 1.5)	Bone Marrow (score point 1)	Lung Metastases (score point 1)	No. of Patients
≤ 3							3
≤ 3						+	2
≤ 3					+		9
≤ 3				+			6
≤ 3				+		+	4
≤ 3				+	+		8
≤ 3			+				5
≤ 3			+			+	2
≤ 3			+		+		2
≤ 3		+					1
≤ 3		+				+	2
≤ 3		+			+		2
≤ 3		+		+			5
≤ 3		+	+				3
≤ 3	+						2
≤ 3	+				+		3
≤ 3	+				+	+	1
≤ 3	+			+			8
≤ 3	+		+				5
≤ 3	+		+			+	2
≤ 3	+		+		+		1
≤ 3	+	+					6
3-< 5				+	+	+	2
3-< 5		+			+	+	4
3-< 5		+		+		+	11
3-< 5		+		+	+		11
3-< 5		+	+			+	2
3-< 5		+	+		+	+	1
3-< 5	+			+		+	10
3-< 5	+			+	+		8
3-< 5	+			+	+	+	7
3-< 5	+	+				+	8
3-< 5	+	+			+		4
3-< 5	+	+			+	+	2
3-< 5	+	+		+			16
3-< 5	+	+	+				7
3-< 5	+	+	+			+	7
3-< 5	+	+	+		+		2
≥ 5		+		+	+	+	7
≥ 5	+	+		+		+	24
≥ 5	+	+		+	+		23
≥ 5	+	+		+	+	+	15
≥ 5	+	+	+		+	+	1

NOTE. Other metastatic sites outside risk model according to multivariate analysis not listed here.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Michael Paulussen, Odile Oberlin, Jean Michon, Ian Lewis, Alan Craft, Heribert Jürgens
Administrative support: Uta Dirksen
Provision of study materials or patients: Ruth Ladenstein, Odile Oberlin, Henk van den Berg, Lars Hjorth, Ian Lewis, Alan Craft
Collection and assembly of data: Ruth Ladenstein, Odile Oberlin, Henk van den Berg, Uta Dirksen, Lars Hjorth, Jean Michon
Data analysis and interpretation: Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Odile Oberlin, Alan Craft
Manuscript writing: Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Jeremy Whelan, Michael Paulussen, Odile Oberlin, Henk van den Berg, Uta Dirksen, Jean Michon, Ian Lewis, Alan Craft
Final approval of manuscript: Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Jeremy Whelan, Michael Paulussen, Odile Oberlin, Henk van den Berg, Uta Dirksen, Lars Hjorth, Jean Michon, Ian Lewis, Alan Craft, Heribert Jürgens

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Acknowledgment

The European Ewing Tumor Working Initiative of National Groups was established by the German Society of Pediatric Oncology and Hematology (Germany), Austrian Group for Pediatric Hemato-Oncology, the Société Française des Cancers de l'Enfant (France), Fédération Nationale de lutte contre le Cancer (France), Children's Cancer and Leukemia Group (United Kingdom), the Swiss Institute of Applied Cancer Research (Switzerland), and the Dutch Childhood Oncology Group (the Netherlands). We thank participating centers and physicians, nurses, and data managers for their continuing patient care and data reporting. In particular, the data centers in Leicester, United Kingdom; Institut Gustave Roussy, Villejuif, France, the University Münster, Germany, and Department of Studies and Statistics for Integrated Research and Projects of the Children's Cancer Research Institute in Vienna/Austria have been involved in data mining, reporting, and analyses throughout the study period.

Appendix

Table A1. Risk Score

Risk Factor	Points
Age, years	
≤ 14	0
> 14	1
Volume, mL	
< 200	0
≥ 200	1.5
Bone metastases	
None	0
1 bone lesion	1
> 1 bone lesion	1.5
BM metastasis	
None	0
Yes	1
Lung metastasis	
None	0
Yes	1
Total maximum score	6

Abbreviation: BM, bone marrow.

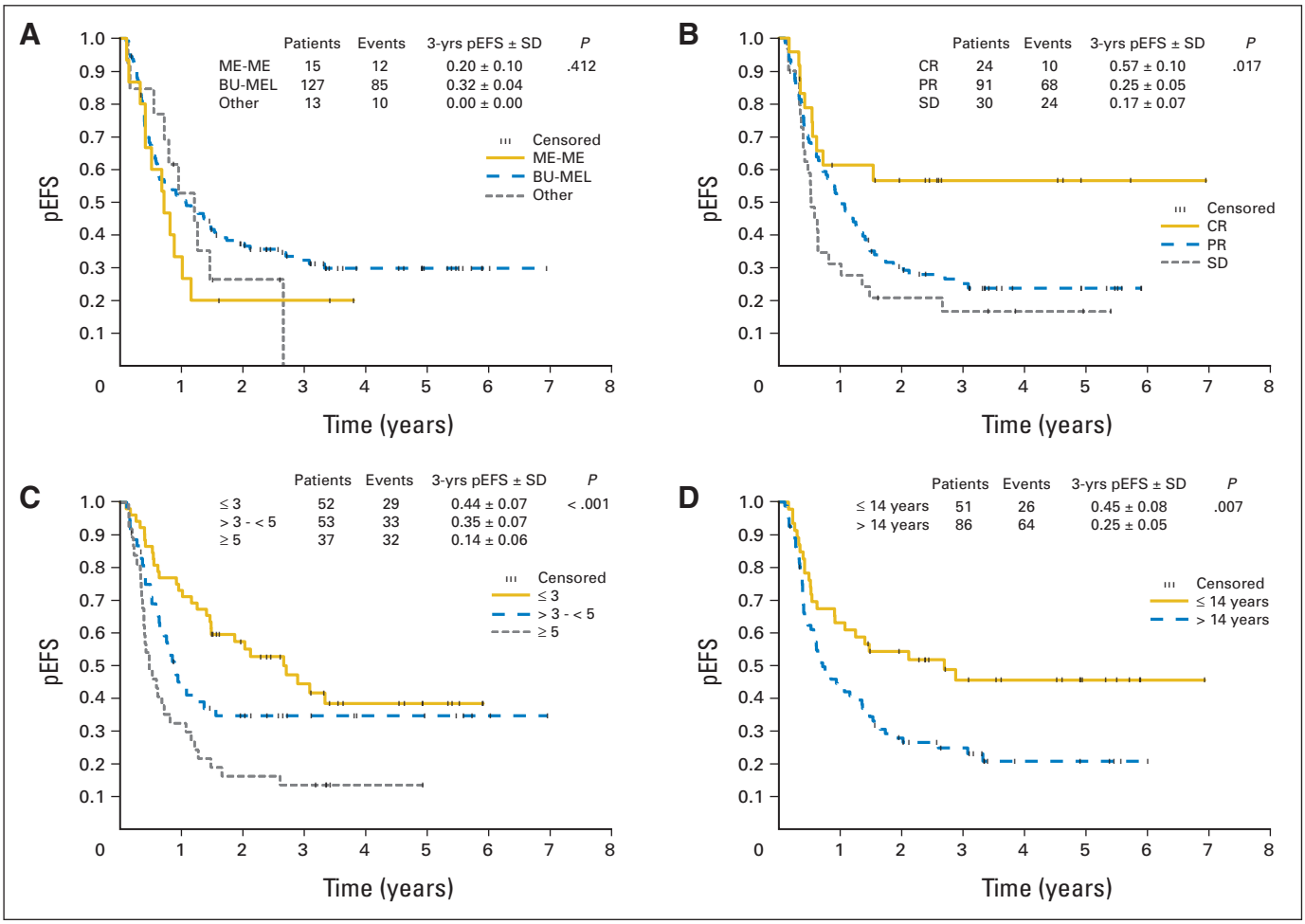

Fig A1. Event-free survival in patients with high-dose therapy (HDT; A) according to HDT, (B) according to response before HDT, (C) according to score group, and (D) according to age group in patients receiving busulfan and melphalan (BU-MEL). Unfortunately, the date of the HDT was missing in 14 patients; these patients were excluded from the comparative analysis of the HDT regimen used. ME-ME, double course of melphalan plus etoposide; CR, complete remission; PR, partial remission; SD, stable disease.

