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original reports

High-Dose Treosulfan and Melphalan as Consolidation Therapy Versus Standard Therapy for High-Risk (Metastatic) Ewing Sarcoma

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abstract

PURPOSE Ewing 2008R3 was conducted in 12 countries and evaluated the effect of treosulfan and melphalan high-dose chemotherapy (TreoMel-HDT) followed by reinfusion of autologous hematopoietic stem cells on event-free survival (EFS) and overall survival in high-risk Ewing sarcoma (EWS).

METHODS Phase III, open-label, prospective, multicenter, randomized controlled clinical trial. Eligible patients had disseminated EWS with metastases to bone and/or other sites, excluding patients with only pulmonary metastases. Patients received six cycles of vincristine, ifosfamide, doxorubicin, and etoposide induction and eight cycles of vincristine, actinomycin D, and cyclophosphamide consolidation therapy. Patients were randomly assigned to receive additional TreoMel-HDT or no further treatment (control). The random assignment was stratified by number of bone metastases (1, 2-5, and > 5). The one-sided adaptive-inverse-normal-4-stage-design was changed after the first interim analysis via Müller-Schäfer method.

RESULTS Between 2009 and 2018, 109 patients were randomly assigned, and 55 received TreoMel-HDT. With a median follow-up of 3.3 years, there was no significant difference in EFS between TreoMel-HDT and control in the adaptive design (hazard ratio [HR] 0.85; 95% CI, 0.55 to 1.32, intention-to-treat). Three-year EFS was 20.9% (95% CI, 11.5 to 37.9) in TreoMel-HDT and 19.2% (95% CI, 10.8 to 34.4) in control patients. The results were similar in the per-protocol collective. Males treated with TreoMel-HDT had better EFS compared with controls: median 1.0 years (95% CI, 0.8 to 2.2) versus 0.6 years (95% CI, 0.5 to 0.9); $P = .035$; HR 0.52 (0.28 to 0.97). Patients age < 14 years benefited from TreoMel-HDT with a 3-years EFS of 39.3% (95% CI, 20.4 to 75.8%) versus 9% (95% CI, 2.4 to 34); $P = .016$; HR 0.40 (0.19 to 0.87). These effects were similar in the per-protocol collective. This observation is supported by comparable results from the nonrandomized trial EE99R3.

CONCLUSION In patients with very high-risk EWS, additional TreoMel-HDT was of no benefit for the entire cohort of patients. TreoMel-HDT may be of benefit for children age < 14 years.

J Clin Oncol 40:2307-2320. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying editorial on page 2288

Data Sharing Statement

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 10, 2022 and published at ascopubs.org/journal/jco on April 15, 2022: DOI https://doi.org/10.1200/JCO.21.01942

INTRODUCTION

Ewing sarcoma (EWS) is a highly aggressive cancer mostly affecting young people. The presence of metastatic disease is the main prognostic factor in EWS. About 20%-25% of patients present with metastases at diagnosis with survival rates of < 30%[1]-60%.[2-4] Prognosis for primary disseminated disease with bone/bone-marrow involvement and more than one bone metastasis is far worse than for patients with pulmonary metastases only[4] or only solitary bone metastasis.[1,3,5] International groups have investigated the value of dose intensification in patients with disseminated disease in either retrospective analyses or nonrandomized treatment recommendations.[6,7] No prospective randomized study has been conducted on the value of high-dose chemotherapy (HDT) followed by autologous hematopoietic stem-cell rescue in EWS.

A prospective study by a group in the United States[8] and a retrospective analysis by a European group investigated the role of consolidation with HDT with melphalan and etoposide (MelEto) plus whole-body irradiation in primary disseminated disease.[8] In the US study, consolidation therapy failed to improve event-free survival (EFS). Two-year EFS was 24% for patients

CONTEXT

Key Objective

Metastatic Ewing sarcoma has a poor prognosis, and conventional treatment failed. The key problem is that conventional combined-modality treatment reduces tumor burden, but typically fails to eradicate residual cancer cells. EWING 2008, a randomized international phase III clinical trial, analyzed the value of additional treosulfan-melphalan high-dose chemotherapy (TreoMel-HDT) followed by autologous stem-cell retransfusion.

Knowledge Generated

The trial demonstrated no benefit from additional high-dose chemotherapy in metastatic patients. However, in a subgroup analysis, a benefit was observed in children age < 14 years.

Relevance

Treatment intensification does not improve the outcome in metastatic Ewing sarcoma. Further studies using novel targeted therapies and improved molecular and genomic tools need to be evaluated in future trials.

who received HDT compared with an EFS of 20% for all eligible patients.[8] The European study showed a 5-year EFS of 22% in patients following MelEto-HDT plus whole-body irradiation and 29% following tandem MelEto-HDT.[9]

The Euro-E.W.I.N.G.99 trial included a nonrandomized arm for patients with extrapulmonary metastatic disease in which all patients received busulfan and melphalan (BuMel)-HDT followed by autologous stem-cell rescue; the 3-year EFS was 27%. The study identified age > 14 years, large primary tumor, and more than one metastatic site as risk factors for unfavorable outcome.[1] An Italian study included a more favorable group of patients with pulmonary metastases[4,10] or solitary bone metastasis.[1] Patients were treated with adjuvant multimodal chemotherapy and local therapy, followed by BuMel-HDT. The 5-year EFS was 43%.[3]

The incompatibility of a BuMel-HDT regimen with radiotherapy to axial sites prompted the search for alternative regimen harmonizing with local treatment, given that local treatment is a decisive therapeutic element in metastatic disease.[5] Treosulfan is a prodrug of a bifunctional alkylating cytotoxic agent and structurally related to busulfan. Treosulfan is frequently used in high-dose protocols followed by allogeneic or autologous hematopoietic stem-cell transplantation/reinfusion. Published studies point out its remarkable safety with very low nonhematologic toxicity in heavily pretreated patients and patients at high risk of treatment-related toxicity.[11] No study has yet been published concerning the effect of treosulfan in EWS. In vitro data showed stronger growth inhibition by treosulfan compared with busulfan in EWS cell lines,[12] and in relapsed EWS patients, treatment with treosulfan-melphalan (TreoMel) was comparable with BuMel in terms of efficacy.[13]

To evaluate the urgent question on the value of HDT to consolidate patients with primary disseminated EWS, patients in the EWING 2008R3 trial were treated with six cycles of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) induction and randomly assigned to consolidation with either eight cycles of vincristine, actinomycin D, and cyclophosphamide (VAC) chemotherapy compared with eight cycles of VAC with additional treosulfan-melphalan HDT (TreoMel-HDT) followed by autologous stem-cell reinfusion.

METHODS

Study Design

The Ewing 2008R3 trial was an international, phase III, open-label, multicenter, randomized, controlled first-line trial of international study groups comparing two consolidation regimens in a parallel-group design: eight VAC cycles versus VAC cycles with TreoMel-HDT and autologous stem-cell reinfusion in patients with high-risk EWS (metastatic disease other than lung; Data Supplement, online only; ClinicalTrials.gov identifier: NCT00987636, EudraCT: 2008-003658-13). The trial was conducted in 91 pediatric and adult oncology centers in 12 countries. Appropriate ethics committees approved the trial in line with the legislation in each country. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Eligibility Criteria

Inclusion criteria were biopsy-proven EWS of bone or soft tissue classified as a high-risk disease, that is, dissemination to bone and/or other sites, and possibly additional pulmonary dissemination. Further criteria were age ≥ 4 and < 50 years, Lansky/Karnofsky score > 50%, hemoglobin > 8 g/dL (transfusion allowed), platelets > 80.000/μL (transfusion allowed), WBC > 2,000/μL, and cardiac values left ventricular ejection fraction > 40% and shortening fraction > 28%. Registration and start of chemotherapy should be ≤ 45 days from diagnostic biopsy/surgery. Exclusion criteria were more than one cycle of chemotherapy before registration, second malignancy, pregnancy or lactation, concurrent treatment within any other clinical trial, or any other conditions incompatible with the protocol treatment. The diagnosis of EWS was based on

morphologic and immunophenotypic criteria, and whenever possible on molecular definition. Written informed consent was obtained from all patients and/or their parents/guardians before enrollment.

Pretreatment Evaluation

The primary tumor volume was measured by using magnetic resonance imaging or computed tomography (CT) scan as appropriate. Staging-investigations included chest CT and positron emission tomogram (-CT/-magnetic resonance imaging) or TC99-scintigraphy, bone-marrow aspirations, and biopsies. Renal function was assessed by tubular phosphate reabsorption and glomerular filtration rate.

Treatment

Induction chemotherapy consisted of six chemotherapy courses of VIDE.[14] Standard consolidation chemotherapy consisted of eight VAC cycles. Patients randomly assigned to additional HDT received TreoMel followed by autologous stem-cell reinfusion. Treosulfan 12 g/m^2 intravenous was given once daily on days –5 to –3 before autologous stem-cell reinfusion (cumulative dose 36 g/m^2). In small children ($<$ 20 kg body weight [BW]), treosulfan was calculated per kg BW (1 m^2 body surface area = 30 kg BW). Melphalan 140 mg/m^2 intravenous was given once on day –2 before stem-cell reinfusion. Timing of TreoMel-HDT consolidation depended on the timing and type of local treatment: local therapy in R3 patients was performed after VIDE induction. Any delay between VIDE and HDT for reasons of local treatment was bridged with VAC cycles. The total number of scheduled VAC cycles was eight. Local therapy was tailored to patient and tumor characteristics and included surgery with complete surgical removal wherever feasible after VIDE cycle six or on hematologic recovery, radiotherapy, or a combination of both (Data Supplement).

Random Assignment

Random assignment was performed centrally at latest after six VIDE courses. The random assignment was balanced and stratified according to the number of bone metastases (0-1, 2-5, and $>$ 5 lesions) using block randomization (block size of four). The randomization envelopes and lists were prepared by the Institute of Biostatistics and Clinical Research, Germany.

End Points and Assessments

The primary end point EFS was defined as the time from random assignment to the date of the first event (progression, relapse, secondary malignancy, or death, whichever occurred first). Follow-up was recommended every 3 months during the first 3 years, every 6 months during years 4 and 5, and then yearly. Secondary efficacy end point was overall survival (OS) from random assignment, considering deaths of all causes. Central imaging review of tumor volume and response and pathologic review were recommended. Compliance with treatment and toxicity were monitored. All chemotherapy doses were recorded, as well as the reasons for dose reduction or delay. Further secondary end points were acute toxicities related to chemotherapy. They were assessed after each course using a list of selected items from the National Cancer Institute Common Toxicity Criteria version 3.0 and Bearman's criteria for sinusoidal obstruction syndrome. A free text area was available to document other acute toxicities. A modified list was used to evaluate toxicity after radiotherapy, using Radiation Therapy Oncology Group classification. For each toxicity item, the analysis was based on the maximum grade observed over the whole consolidation treatment duration (combining toxicities reported on consolidation [VAC] and HDT forms). Toxicities from radiation therapy were not regarded in this manuscript. Grade 4 hematologic toxicities and grade $\geq$ 3 nonhematologic toxicities were classified as severe (Data Supplement).

Statistics

The primary aim of the randomized Ewing 2008R3 trial was to examine whether TreoMel-HDT in addition to VIDE induction and VAC consolidation chemotherapy improves EFS in patients with disseminated EWS compared with VAC consolidation alone. The study was designed to ensure 80% power to detect a difference between the TreoMel-HDT and the standard VAC arm in the primary end point EFS from random assignment (expected 3-year EFS: 30% *v* 15%, hazard ratio [HR] 0.635) within an adaptive design with one-sided significance level 5%. Initially, a one-sided equally spaced four-stage group sequential design with O'Brien and Fleming[15] boundaries using log-rank tests was planned, and changed to an adaptive design using the inverse normal combination function.[16,17] Assuming exponential distributed event times, accrual time of 5 years, follow-up time of 2 years, and 5% dropouts, the initial target sample size was 185 patients to observe 155 necessary events. With support from the independent data monitoring committee, recruitment was stopped before reaching this target. On the basis of data of the first interim analysis, the design was changed to perform one additional final analysis using the conditional error rejection probability method[18] (Data Supplement). This is the final analysis on the basis of data as of June 2019. Survival rates (EFS and OS) were estimated using the Kaplan-Meier[19] method with two-sided 95% CIs using log-transformation. Median follow-up was estimated using the reverse Kaplan-Meier method.[19] HRs and 95% CIs for EFS and OS were estimated by using Cox regression analysis.[20] The primary efficacy analysis was performed according to the intention-to-treat (ITT) principle. Sensitivity analyses were performed using multivariable Cox regression models including the treatment effect and adjusting for number of bone metastases (0-1, 2-5, and $>$ 5 lesions), sex, and age (years). Analyses were repeated in the per-protocol and safety collective. Competing risk approaches were used for EFS to estimate the effect of treatment on the cumulative incidence,[21] subdistribution hazard,[22] and cause-specific hazard[23] of each competing

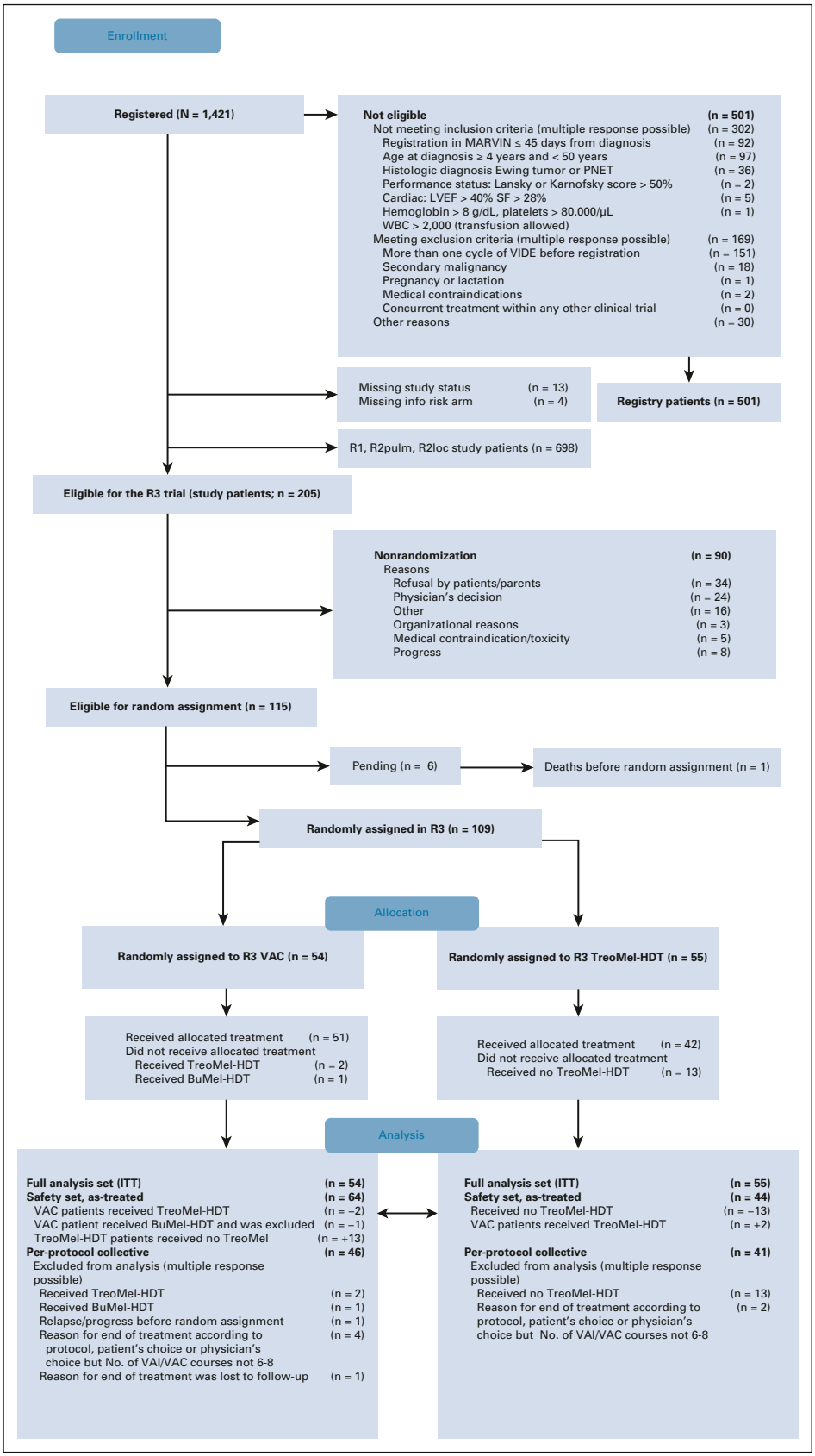

FIG 1. CONSORT flowchart. BuMel, busulfan and melphalan; HDT, high-dose chemotherapy; ITT, intention-to-treat; LVEF, left ventricular ejection fraction; PNET, peripheral neuroectodermal tumor; SF, shortening fraction; TreoMel, treosulfan-melphalan; VAC, vincristine, actinomycin D, and cyclophosphamide; VAI, vincristin, actinomycin D, ifosfamid; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide.

TABLE 1. Patient and Tumor Baseline Characteristics

Characteristic	Full Analysis Set (ITT)			Per-Protocol Set		Safety Set (as-treated)	
	Total (N = 109)	VAC (n = 54)	TreoMel-HDT (n = 55)	VAC (n = 46)	TreoMel-HDT (n = 41)	VAC (n = 64)	TreoMel-HDT (n = 44)
Sex, No. (%)							
Male	54 (50)	23 (43)	31 (56)	17 (37)	23 (56)	29 (45)	25 (57)
Female	55 (50)	31 (57)	24 (44)	29 (63)	18 (44)	35 (55)	19 (43)
Age, years							
Median (range)	15.8 (4.4-45.4)	15.1 (4.8-45.4)	16.6 (4.4-43.8)	14.8 (4.8-36.6)	15.0 (4.4-43.8)	16.4 (4.8-45.4)	15.1 (4.4-43.8)
Follow-up since random assignment, years							
Median duration (KM Est, 95% CI)	3.3 (2.4 to 4.2)	2.8 (2.2 to 4.6)	3.3 (2.2 to 5.2)	2.8 (2.2 to 4.6)	4.2 (2.2 to 5.6)	2.8 (2.2 to 4.2)	3.8 (2.2 to 5.6)
Range (min-max)	0-8.0	0-8.0	0.2-6.1	0.4-6.1	0.3-8.0	0-6.1	0.3-8.0
Primary tumor origin, No. (%)							
Pelvis	65 (60)	34 (63)	31 (57)	28 (61)	24 (60)	38 (59)	26 (60)
No pelvis	43 (40)	20 (37)	23 (43)	18 (39)	16 (40)	26 (41)	17 (40)
Unknown primary	1		1		1		1
Primary tumor site, No. (%)							
Pelvis	43 (40)	20 (37)	23 (43)	18 (39)	16 (40)	26 (41)	17 (40)
Abdomen	3 (3)	1 (2)	2 (4)	1 (2)	2 (5)	1 (2)	2 (5)
Spine	9 (8)	2 (4)	7 (13)	2 (4)	4 (10)	5 (8)	4 (9)
Chest	21 (19)	12 (22)	9 (17)	9 (20)	7 (18)	12 (19)	8 (19)
Head/neck	4 (4)	2 (4)	2 (4)	2 (4)	1 (3)	3 (5)	1 (2)
Upper extremity	4 (4)	3 (6)	1 (2)	1 (2)	1 (3)	2 (3)	2 (5)
Lower extremity	24 (22)	14 (26)	10 (19)	13 (28)	9 (23)	15 (23)	9 (21)
Unknown primary	1		1		1		1
Metastatic disease at diagnosis, No. (%)	109 (100)	54 (100)	55 (100)	46 (100)	41 (100)	64 (100)	44 (100)
Lung metastases, No. (%)	58 (53)	31 (57)	27 (49)	29 (63)	19 (46)	37 (58)	20 (46)
Bone metastases, No. (%)	86 (79)	41 (76)	45 (82)	35 (76)	32 (78)	50 (78)	35 (80)
Bone metastases, No. (%)							
Single lesion	22 (26)	10 (24)	12 (27)	10 (29)	8 (25)	14 (28)	8 (23)
2-5 lesions	24 (28)	11 (27)	13 (29)	8 (23)	9 (28)	14 (28)	10 (29)
> 5 lesions	40 (46)	20 (49)	20 (44)	17 (49)	15 (47)	22 (44)	17 (49)
Clinical response of primary tumor to initial chemotherapy at the date of random assignment, No. (%)							
Complete or partial remission	95 (90)	48 (92)	47 (89)	41 (93)	36 (90)	55 (90)	39 (91)
Stable disease	9 (9)	4 (8)	5 (9)	3 (7)	4 (10)	5 (8)	4 (9)
Progressive disease	1 (1)	0	1 (2)	0	0	1 (2)	0
Not measured or not applicable	4	2	2	2	1	3	1

(continued on following page)

TABLE 1. Patient and Tumor Baseline Characteristics (continued)

Characteristic	Full Analysis Set (ITT)			Per-Protocol Set		Safety Set (as-treated)	
	Total (N = 109)	VAC (n = 54)	TreoMel-HDT (n = 55)	VAC (n = 46)	TreoMel-HDT (n = 41)	VAC (n = 64)	TreoMel-HDT (n = 44)
Clinical response of metastases (worst grade) to initial chemotherapy at the date of random assignment, No. (%)							
Complete or partial remission	83 (80)	43 (84)	40 (75)	36 (84)	30 (77)	49 (80)	33 (79)
Stable disease	21 (20)	8 (16)	13 (25)	7 (16)	9 (23)	12 (20)	9 (20)
Not measured or not applicable	5	3	2	3	2	3	2
Local treatment of primary tumor (planned or completed) at the date of random assignment, No. (%)							
Resection after chemotherapy alone ± late radiotherapy	44 (42)	24 (45)	20 (38)	20 (44)	15 (39)	27 (43)	16 (39)
Resection at diagnosis	6 (6)	0 (0)	6 (12)	0 (0)	4 (11)	2 (3)	4 (10)
Radiotherapy alone, early radiotherapy (tumor unresectable)	17 (16)	5 (9)	12 (23)	3 (4)	9 (24)	7 (11)	10 (24)
Radiotherapy alone, late radiotherapy (tumor unresectable)	29 (28)	18 (34)	11 (21)	16 (36)	9 (24)	19 (30)	10 (24)
Other	9 (9)	6 (11)	3 (6)	6 (13)	1 (3)	8 (13)	1 (2)
Not applicable	4	1	3	1	3	1	3
Primary tumor histologic response among patients who underwent surgery after chemotherapy, No. (%)							
Good	26	16 (70)	10 (59)	13 (68)	8 (62)	16 (64)	9 (64)
Poor	14	7 (30)	6 (41)	6 (32)	5 (38)	9 (36)	5 (36)
Missing data or not applicable	7	1	6	1	4	3	4
Extrapulmonary metastases histologic response among patients who underwent surgery, No. (%)							
Good	10 (73)	7 (100)	3 (60)	7 (100)	2 (50)	8 (100)	2 (50)
Poor	2 (17)	0 (0)	2 (40)	0 (0)	2 (50)	0 (0)	2 (50)

NOTE. Because of rounding of the values, the percentages do not always add up to exactly 100%.

Abbreviations: HDT, high-dose chemotherapy; ITT, intention-to-treat; KM Est, Kaplan-Meier estimate; TreoMel, treosulfan-melphalan; VAC, vincristine, actinomycin D, and cyclophosphamide.

event: locoregional recurrence/local progression, new metastases/metastatic progression, combined relapse/progression, secondary malignancy, and death. All analyses reported in the text were performed in the full analysis set (ITT), except for the safety analyses, which were performed in the safety set (as-treated). Data preparation and unadjusted analysis were performed using SAS software, Version 9.4 TS1M5, of the SAS System for Windows, and adaptive analyses using ADDPLAN v6.1.1 and R v3.6.0 using the package rpact v2.0.1.

TABLE 2. Event-Free and Overall Survival

Outcome	Full Analysis Set (ITT)		Per-Protocol Set[a]		Safety Set (as-treated)[b]	
	VAC (n = 54)	TreoMel-HDT (n = 55)	VAC (n = 46)	TreoMel-HDT (n = 41)	VAC (n = 64)	TreoMel-HDT (n = 44)
EFS since random assignment						
No. and type of events	43	39	35	31	48	33
Estimates						
Median EFS, years (KM Est, 95% CI)	0.9 (0.6 to 1.1)	1.1 (0.8 to 1.8)	0.9 (0.6 to 1.4)	1.1 (0.9 to 2.1)	0.7 (0.6 to 1.1)	1.1 (0.9 to 2.1)
1-year EFS (KM Est, 95% CI)	39.8 (28.6 to 55.4)	51.8 (39.7 to 67.5)	42.5 (30.2 to 59.7)	57.5 (43.9 to 75.2)	39.3 (28.7 to 53.8)	55.7 (42.6 to 72.9)
3-year EFS (KM Est, 95% CI)	19.2 (10.8 to 34.4)	20.9 (11.5 to 37.9)	22.7 (12.8 to 40.1)	18.1 (8.6 to 38.2)	21.0 (12.6 to 35.0)	19.6 (10.0 to 38.5)
HR of event (95% CI)[c]	Ref	0.82 (0.53 to 1.27), $P = .3741$	Ref	0.83 (0.51 to 1.35), $P = .4463$	Ref	0.74 (0.48 to 1.16), $P = .1837$
Result of the confirmatory analysis, adaptive design[d]	—	Not significant	—	—	—	—
Multivariable HR of event (95% CI)[e]	Ref	0.72 (0.46 to 1.12), $P = .1400$	Ref	0.69 (0.41 to 1.15), $P = .1502$	Ref	0.61 (0.39 to 0.96), $P = .0344$
Type of first event						
Locoregional recurrence/local progress	2	5	2	4	3	4
New metastases/metastatic progress	26	24	22	49	29	20
Combined relapse/progress	9	10	7	8	11	8
Secondary malignancy	3	0	2	0	2	1
Death as first reported event[f]	3	0	2	0	3	0
OS since random assignment						
No. of deaths	31	30	23	23	35	25
Survival estimates						
3-year OS (KM Est, 95% CI)	37.4 (25.5 to 54.7)	43.4 (30.7 to 61.3)	45.2 (31.8 to 64.4)	46.7 (32.4 to 67.3)	37.4 (26.1 to 53.5)	45.9 (32.2 to 65.5)
5-year OS (KM Est, 95% CI)	33.6 (21.8 to 51.9)	26.8 (14.8 to 48.6)	40.7 (27.0 to 61.3)	28.9 (15.8 to 52.9)	34.0 (22.7 to 50.9)	28.4 (15.6 to 51.7)
HR of death (95% CI)[c]	Ref	0.96 (0.58 to 1.58), $P = .8680$	Ref	1.05 (0.59 to 1.87), $P = .8779$	Ref	0.87 (0.52 to 1.45), $P = .5905$
Multivariable HR of event (95% CI)[e]	Ref	0.82 (0.49 to 1.4), $P = .4638$	Ref	0.87 (0.47 to 1.60), $P = .6425$	Ref	0.68 (0.40 to 1.16), $P = .159$
Cause of deaths						
Because of cancer	28	30	22	23	34	24
Treatment-related[g]	1	0	0	0	0	0
Secondary malignancy	1	0	0	0	0	1
Other cause[h]	1	0	1	0	1	0

Abbreviations: BuMel, busulfan and melphalan; EFS, event-free survival; HDT, high-dose chemotherapy; HR, hazard ratio; ITT, intention-to-treat; KM Est, Kaplan-Meier estimate; OS, overall survival; TreoMel, treosulfan-melphalan; VAC, vincristine, actinomycin D, and cyclophosphamide.

[a]Per-protocol: excluding 22 patients (eight in the VAC arm and 14 in the TreoMel-HDT arm) with major protocol deviation (Fig 1, Data Supplement).

[b]Safety set (as-treated): patients were analyzed regarding the treatment they actually received. One patient was excluded from the TreoMel-HDT arm because of receiving BuMel HDT instead of TreoMel-HDT (Fig 1).

[c]HRs with their 95% CIs are estimated in Cox regression models including only the treatment effect as covariable. *P* values are from univariate two-sided log-rank tests.

[d]The specification of the statistical adaptive design, the design change, and the detailed results of the interim analysis and final analysis are provided in the Data Supplement.

[e]HRs with their 95% CIs and Wald *P* values are estimated in Cox regression models including the treatment effect, number of bone metastases categories (0-1, 2-5, and > 5), sex, and age (years) as covariables.

[f]The three deaths as first events are detailed in the Data Supplement.

[g]The patient died of fulminant sepsis because of neutropenia presumably on the basis of progressive bone marrow involvement. The patient received BuMel-HDT instead of VAC only, on the basis of physician's choice. Details of treatment are provided in the Data Supplement.

[h]The patient died of acute pulmonary embolism without evidence of local recurrence. Details of treatment are provided in the Data Supplement.

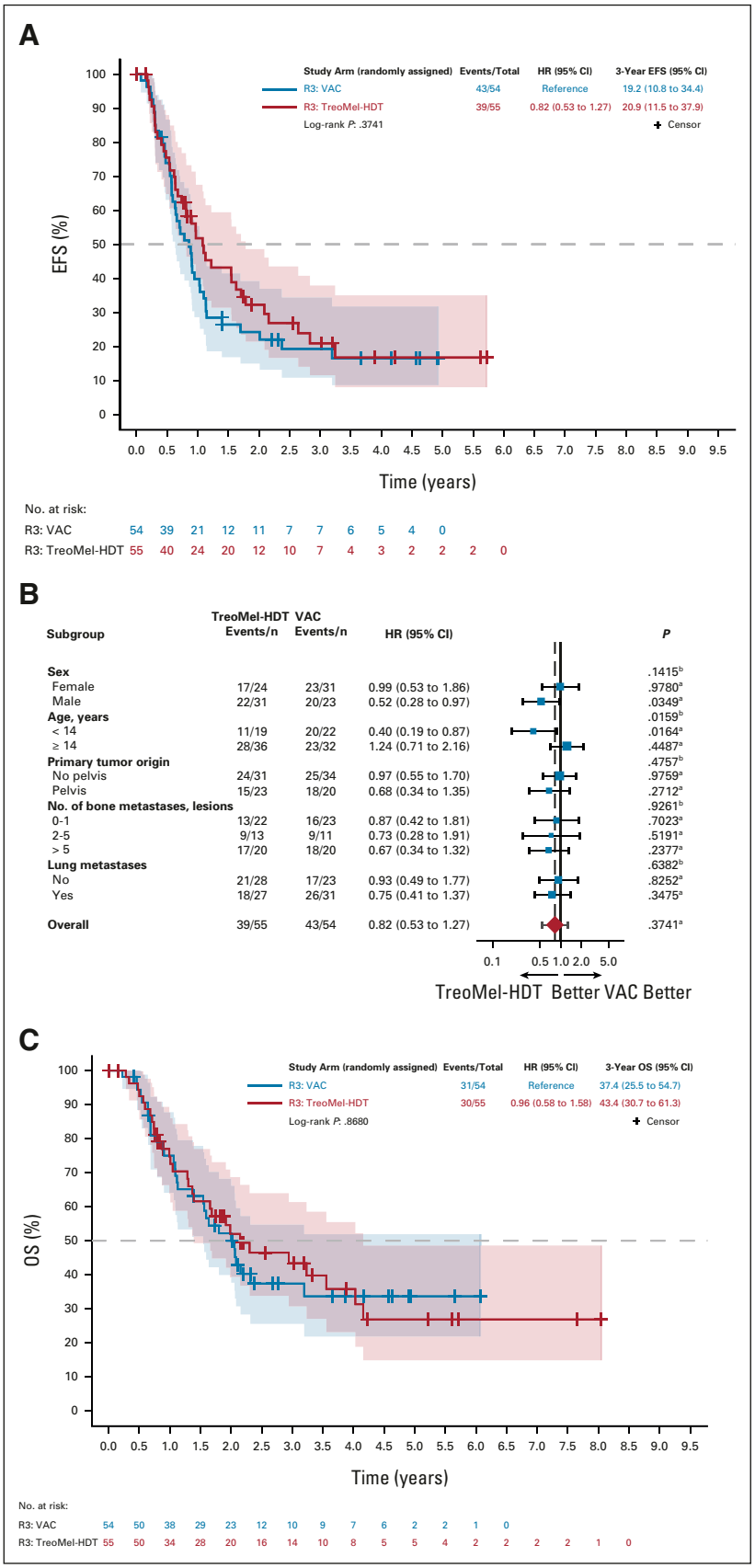

FIG 2. (A) Kaplan-Meier curves with pointwise 95% confidence limits of EFS by treatment group in the full analysis set (ITT). At the time of this (continued on following page)

FIG 2. (Continued). analysis (cutoff date: June 30, 2019), 82 events were reported: 39 in the TreoMel-HDT group and 43 in the VAC group. (B) Forest plot of EFS from random assignment in the full analysis set (ITT) according to subgroups including all randomly assigned patients. The HRs for the comparison of TreoMel-HDT versus VAC were estimated in Cox proportional hazard models within each subgroup. [a]The *P* values were obtained from two-sided log-rank tests or from [b]the Wald test for the treatment and subgroup interaction term from a Cox model with the covariates treatment group, the respective subgroup, and the interaction term. (C) Kaplan-Meier curves with pointwise 95% confidence limits of OS from random assignment by treatment group in the full analysis set (ITT). EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; TreoMel-HDT, treosulfan-melphalan high-dose chemotherapy; VAC, vincristine, actinomycin D, and cyclophosphamide.

RESULTS

Patients

Between October 2009 and February 2018, 1,421 patients enrolled in the Ewing 2008 trial from 120 centers in 12 countries, and were assessed for eligibility (Fig 1). Of 205 potentially eligible R3 patients, 90 were not eligible for the randomized trial because of patient/parent refusal (n = 34), physician refusal (n = 24), organizational reason (n = 3), medical contraindication (n = 5), progressive disease (n = 8), or other reasons (n = 16). Six patients were pending for random assignment, and one of them died before random assignment. Thus, 109 R3 patients from 58 centers were randomly assigned: 55 to TreoMel-HDT and 54 to the VAC arm. Of the 55 patients allocated to the TreoMel-HDT, 13 patients did not receive the randomized HDT, whereas two patients randomly assigned to the VAC control arm received TreoMel-HDT because of physician choice/clinical decision. These 15 patients were included in the respective treatment group of the safety set, but were excluded in the per-protocol analysis. One patient received HDT with BuMel and was excluded from the per-protocol and safety analysis. For other major protocol violations leading to exclusion, see Figure 1, and for treatment details, see the Data Supplement.

Median age at registration was 15.8 years (range, 4.4-45.4 years). There were slightly more males in the TreoMel-HDT arm compared with the control arm (56% *v* 43%). Other baseline characteristics were well balanced between arms (Table 1). Median follow-up since random assignment was 3.3 years (maximum 8.0 years) and similar between treatment arms (Data Supplement).

Efficacy

A total of 82 events were reported (39 in the TreoMel-HDT arm and 43 in the VAC only arm): seven local progressions or local relapses, 50 new metastases or metastatic progression, 19 combined local relapse and metastatic progression, three secondary malignancies, and three deaths as first events (Table 2). The confirmatory efficacy analysis with the adaptive design of the primary end point EFS since random assignment could not show a significant difference between both treatment arms (ITT, Data Supplement). The HR for the comparison of TreoMel-HDT versus VAC was 0.72 (95% CI, 0.46 to 1.12; $P = .37$, univariate log-rank test). The EFS rates at 1 and 3 years were, respectively, 51.8% (95% CI, 39.7 to 67.5) and 20.9% (95% CI, 11.5 to 37.9) in the TreoMel-HDT arm compared with 39.8% (95% CI, 28.6 to 55.4) and 19.2% (95% CI, 10.8 to 34.4) in the VAC arm (Fig 2A). The treatment effect was similar in the multivariable sensitivity analysis adjusted for number of bone metastases, sex, and age, as well as in the analyses conducted in the per-protocol and safety set. In a subgroup analysis, we observed a benefit of TreoMel-HDT in patients age younger than 14 years (HR 0.40; 95% CI, 0.19 to 0.87; treatment-sex interaction $P = .0159$, Fig 2B, Data Supplement). The distribution of prognostic factors in randomly assigned patients age < 14 years was similar to that of nonrandomized patients age < 14 years (Data Supplement). In an additional multivariable Cox regression, the interaction between treatment and age group was still observed (Data Supplement). A similar subgroup effect was seen in male patients (HR 0.52; 95% CI, 0.28 to 0.97), whereas the treatment effect was not statistically noticeably different in males compared with females (interaction $P = .142$). No difference in the treatment effect was found within the categories of primary tumor origin, number of bone metastases, and lung metastases. When considering the different types of first events in the competing risk approach, no difference of the cumulative incidences or of the cause-specific hazards was observed between both arms (Data Supplement).

Concerning the secondary end point OS since random assignment, we did not observe a statistically noticeable benefit of TreoMel-HDT: 61 deaths were reported (30 in the TreoMel-HDT arm and 31 in the VAC arm), leading to an HR of 0.96 (95% CI, 0.58 to 1.58; $P = .87$ log-rank test). OS rates for TreoMel-HDT and VAC were 43.4% (95% CI, 30.7 to 61.3) versus 37.4% (95% CI, 25.5 to 54.7) at 3 years, and 26.8% (95% CI, 14.8 to 48.6) versus 33.6% (95% CI, 21.8 to 51.9) at 5 years, respectively (Table 2 and Fig 2C). The cause of death was EWS in 58 cases. In the VAC arm, one patient died of pulmonary embolism; one patient randomly assigned to the VAC arm, but received

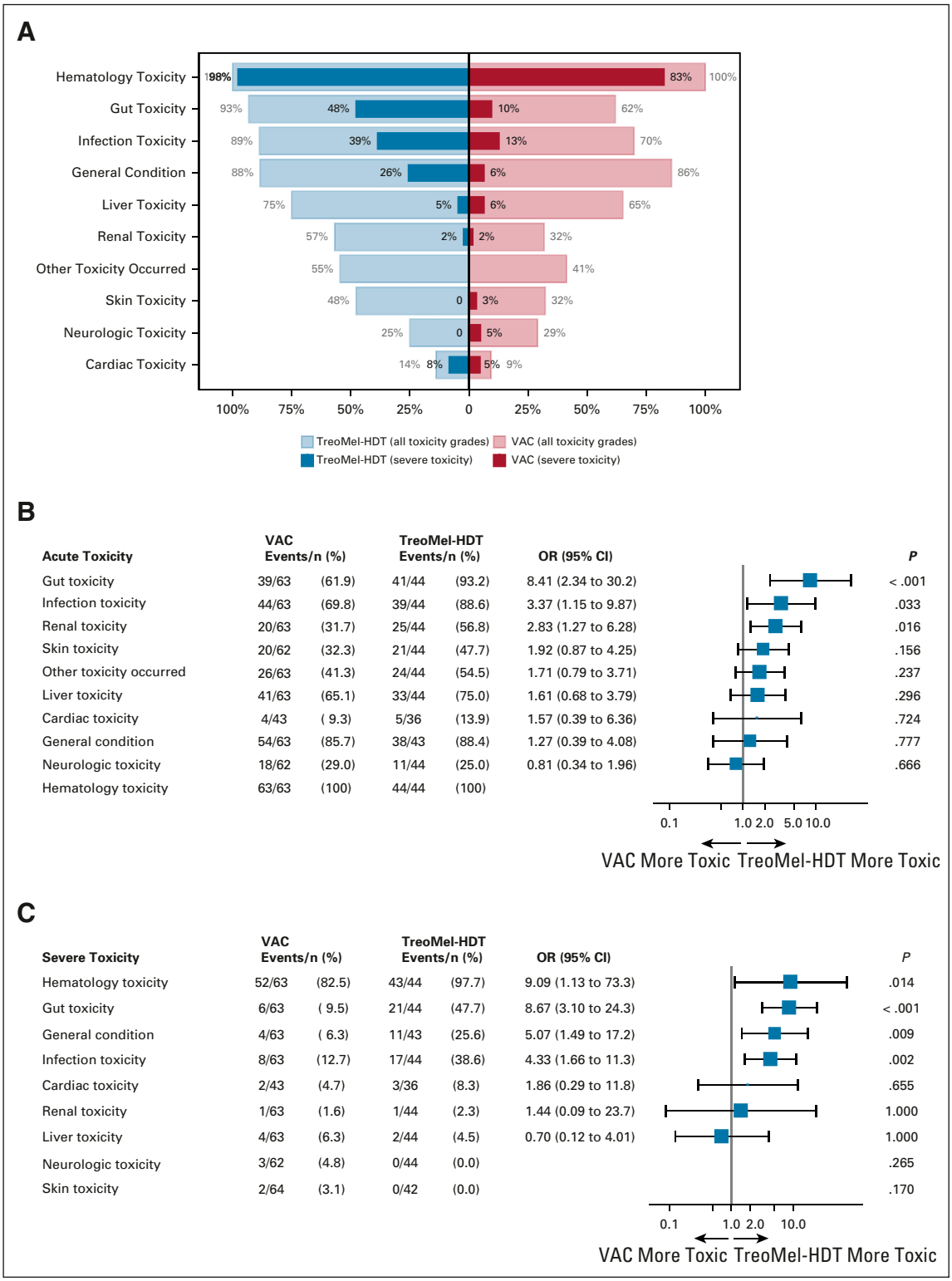

FIG 3. Acute toxicities. (A) The butterfly plot showing the proportion of patients experiencing an acute toxicity, whatever the grade (light blue for TreoMel-HDT and light red for VAC arm), and a severe toxicity (dark blue for TreoMel-HDT and dark red for VAC arm) according to the treatment group (as-treated, safety set). The forest plots display the number of toxicities and the odds ratio of (B) an acute toxicity, whatever the grade, or of (C) a severe toxicity in patients who received TreoMel-HDT relative to patients who received VAC therapy. *P* values are from Fisher's exact tests. Toxicity items are ordered by descending odds ratios. The acute toxicity related to chemotherapy was assessed after each course, using a list of selected items from the National Cancer Institute Common Toxicity Criteria version 3.0. A free text area was available to document other toxicities. The toxicity items were (continued on following page)

FIG 3. (Continued). then pooled by category: hematologic toxicity, infection or fever, gut toxicity, skin toxicity, renal toxicity, liver toxicity, neurologic toxicity, cardiac toxicity, lung toxicity, and general condition. Lung toxicities were only documented during HDT. Details are provided in the Data Supplement. For each toxicity item, the analysis is based on the maximum grade observed over the whole consolidation treatment duration (combining toxicities reported on consolidation [VAI/VAC]) and high-dose treatment forms. Toxicities from radiation therapy were not regarded. Grade 4 hematologic toxicities and grade ≥ 3 nonhematologic toxicities were classified as severe toxicities. This as-treated analysis was performed on the safety set (44 TreoMel-HDT and 64 VAC patients). One patient randomly assigned to VAC was excluded because he received BuMel-HDT. Patients with missing data for a specific toxicity evaluation were excluded for this toxicity. BuMel, busulfan and melphalan; HDT, high-dose chemotherapy; OR, odds ratio; TreoMel, treosulfan-melphalan; VAC, vincristine, actinomycin D, and cyclophosphamide.

TreoMel-HDT, died of secondary malignancy; and one patient randomly assigned to the VAC arm received additional BuMel-HDT and died because of a sepsis (Data Supplement).

Toxicities

All patients developed hematologic toxicity (Fig 3A). Noticeably more infections, gut and renal toxicities were observed during consolidation therapy in the TreoMel-HDT group ($P < .05$; Fig 3B). Of the documented severe toxicities, hematologic, gut, general condition, and infection toxicities occurred more frequently in the TreoMel-HDT arm ($P < .05$; Fig 3C). Details of the maximal toxicity grades, which occurred during consolidation therapy, are given in the Data Supplement. There were no treatment-related deaths because of TreoMel-HDT or VAC therapy only, except for the one patient who received VAC and BuMel-HDT.

DISCUSSION

We report the results of the first randomized trial, conducted to answer the question on the value of additional HDT in patients with primary disseminated EWS. The highly intense treatment schedule of standard chemotherapy plus HDT was manageable with acceptable toxicity. Only one treatment-related death was reported because of a non–protocol-conform BuMel-HDT. The TreoMel-HDT did not improve the survival in this group of very high-risk patients. We observed a potential benefit for TreoMel-HDT consolidation in patients age < 14 years, and the distribution of prognostic factors[1] was balanced in the treatment arms and similar to those of nonrandomized patients. We cannot assume that HDT consolidation would achieve similar benefit for patients who received a more intensive initial therapy. Our results are in concordance with the findings from the nonrandomized study Euro-E.W.I.N.G 99R3 (EE99R3), where 37 patients age < 14 years achieved a 3-year EFS from the time of diagnosis of 47% compared with older patients with 22%.[1] In contrast to the present trial, the EE99R3 study excluded patients with large pelvic tumors and other central axial tumors as radiotherapy to these sites was deemed incompatible with BuMel-HDT for toxicity reasons.[1] A retrospective analyses in patients with first relapse EWS showed a benefit from BuMel-HDT or TreoMel-HDT in patients with response to standard relapse chemotherapy regimen with a 2-year EFS of 44% and 31%, respectively, without additional HDT.[13] All in all, despite dose intensification, patients with advanced disease or at relapse have limited chance to survive.[13,24] Studies of allogeneic stem-cell transplant from HLA-matched or haploidentical donors demonstrated that high-intensity conditioning was more likely to lead to death from complications than reduced-intensity conditioning. Allogeneic stem cell transplantation did not improve survival, with a 5-year OS of only 10%-15%.[25]

Cure of EWS depends largely on eradication of the disease during initial therapy. To date, patients are stratified by clinical parameters at the time of diagnosis, such as metastases or tumor volume and yet, no validated tools for early detection on patient-important outcomes or early detection of relapse are available. Early detection of treatment failure and relapse may turn the page from a fatal to a curative disease, and recent advances on detection and quantification[26] raise the hope that in the future, easy-to-use tools for assessment of treatment response and minimal disease monitoring may be available. First results implicate that deep molecular analysis of cell-free DNA enables comprehensive classification on the basis of genetic and epigenetic profiling.[27]

Phase II trials on tyrosine kinase inhibitors showed promising results in heavily pretreated patients with a 26% overall response rate with cabozantinib[28] and a 10% overall response rate with regorafenib.[29] Novel agents such as the lysine-specific demethylasese-1 inhibitor seclidemstat are under investigation,[30] and the RNA helicase inhibitor TK216 showed first promising results in a phase I trial.[31] Ganitumab, an insulin-like growth factor receptor monoclonal antibody inhibitor was evaluated in combination with interval-compressed vincristin, doxorubicin, cyclophosphamide/ifosfamide, etoposide in a randomized phase II study by the Children's Oncology Group.[32] Insulin-like growth factor receptor inhibitors have an approximately 10% response rate as monotherapy in relapsed EWS.[33,34] Preliminary results did not demonstrate an improvement in survival with the addition of ganitumab.[32]

In conclusion, TreoMel-HDT has a favorable toxicity profile, but did not result in improved outcomes compared with standard chemotherapy in patients with disseminated metastatic EWS. Further studies using novel targeted therapies and improved molecular and genomic tools to detect relapse are required and will be evaluated in the upcoming iEuro-Ewing trial.

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PRIOR PRESENTATION

Presented in part ASCO Virtual Annual Meeting, May 29-31, 2020; and the International Society of Pediatric Oncology Virtual Annual Meeting, October 14-17, 2020.

SUPPORT

Supported by Deutsche Krebshilfe (70-2551-Jue3 and 108128); sponsor: University Hospital Muenster.

CLINICAL TRIAL INFORMATION

Registered in the trial registry ClinicalTrials.gov identifier: NCT00987636 and EudraCT: 2008-003658-13.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.01942.

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Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

High-Dose Treosulfan and Melphalan as Consolidation Therapy Versus Standard Therapy for High-Risk (Metastatic) Ewing Sarcoma

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.