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ORIGINAL ARTICLE

Irinotecan and temozolomide in recurrent Ewing sarcoma: an analysis in 51 adult and pediatric patients

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ABSTRACT

Background: Data on temozolomide (TEM) and irinotecan (IRI) activity in recurrent Ewing sarcoma (EWS), especially in adult patients, are limited.

Methods: Patients receiving TEM 100 mg/m^2/day oral, and IRI 40 mg/m^2/day intravenous, days 1–5, every 21 days, were included in this multi-institutional retrospective study. Disease control rate (DCR) [overall response rate (ORR) [complete response (CR) + partial response (PR)] + stable disease (SD)], 6-months progression-free survival (6-mos PFS) and 1-year overall survival (OS) were assessed.

Results: The median age of the 51 patients was 21 years (range 3–65 years): 34 patients (66%) were adults (≥18 years of age), 24 (48%) had ECOG 1 and 35 (69%) were presented with multiple site recurrence. TEMIRI was used at first relapse/progression in 13 (25%) patients, while the remainder received TEMIRI for second or greater relapse/progression. Fourteen (27%) patients had received prior myeloablative therapy with busulfan and melphalan. We observed five (10%) CR, 12 (24%) PR and 19 (37%) SD, with a DCR of 71%. 6-mos PFS was 49% (95% CI 35–63) and it was significantly influenced by ECOG (6-mos PFS 64% [95% CI 45–83] for ECOG 0, 34% [95% CI 14–54] for ECOG ≥1; $p = .006$) and LDH (6-mos PFS 62% [95% CI 44–79] for normal LDH, 22% [95% CI 3–42] for high LDH; $p = .02$), with no difference according to line of treatment, age and metastatic pattern. One-year OS was 55% (95% CI 39–70), with RECIST response ($p = .001$) and ECOG ($p = .0002$) independently associated with outcome. Grade 3 and 4 toxicity included neutropenia in 12% of patients, thrombocytopenia in 4%, diarrhea in 4%.

Conclusions: This series confirms the activity of TEMIRI in both adults and pediatric patients. This schedule offers a 71% DCR, independently of the line of chemotherapy. Predictive factors of response are ECOG and LDH.

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Introduction

Ewing sarcoma (EWS) is a malignant, small round cell tumor of bone and soft tissue with varying degrees of neuroectodermal differentiation, and pathognomonic translocations [1]. Since the introduction of multi-agent chemotherapy schedules, approximately 70% of patients with localized disease are cured with a combination of systemic and local therapies [2–4].

However, the outcome of patients with recurrent EWS remains poor with 5-year overall survival (OS) ranging from 8% to 15% in different series [5–9] Various chemotherapy regimens have been evaluated in this setting including high-dose chemotherapy with stem cells rescue [10], alkylating agents [11,12], camptothecin derivatives [13,14] and platinum agents [15]. Only few salvage schedules have emerged for 'routine' use, including cyclophosphamide and topotecan [16,17] as well as temozolomide and irinotecan (TEMIRI), gemcitabine and docetaxel (GEM-TXT) [18,19], and high-dose ifosfamide (HDIFO) [20,21]. Most of the available data regarding the activity and toxicity of TEMIRI are from retrospective studies on pediatric EWS populations (Table 1) [13,22–30].

Therefore, the aim of this study was to study the efficacy and safety profile of the TEMIRI schedule, and to identify factors predictive of response for pediatric and adult EWS patients treated with this combination in different European referral centers.

Material and methods

A joint retrospective analysis between the Italian Sarcoma Group and the Royal Marsden Hospital was planned, in order to collect data on patients with recurrent EWS treated with TEMIRI.

The study was approved by the institutional review board of all five participating centers: four Italian referral centers (Rizzoli Institute, Bologna; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; IRCCS Candiolo, Torino; OIRM, Torino)

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Table 1. Response rate (RR) to different temozolomide and irinotecan combination in Ewing sarcoma.

	Phase	No. pts	Median age, years (range)	CR/PR	RR	TMZ (mg/m^2)	irinotecan (mg/m^2) × days × week	Other agents
Wagner et al. (PBC 2007) [13]	R	16	18 (7–33)	1/3	29%	100 × 5	IV 10–20 × 5 × 2	None
Casey et al. (PBC 2009) [22]	R	19	19.5 (2–40)	5/7	63%	100 × 5	IV 20 × 5 × 2	None
Hernandez-Marques et al. (An Ped 2013) [23]	R	8	13 (6–18)	0/3	37%	80–100 × 5	IV 10–20 × 5 × 2	None
Raciborska et al. (PBC 2013) [24]	R	22	14.3	5/7	54%	125 × 5	IV 50 × 5	VCR
McKnall-Knapp et al. (PBC 2010) [25]	I	1	Na	0/1	100%	100 × 5	IV 20 × 5 × 2	VCR
Wagner et al. (PBC 2010) [26]	I	5	Uk (<21)	1/1	40%	100–150 × 5	PO 35–90 × 5 PO 35–90 × 5 × 2	VCR
Wagner et al. (PBC 2013) [27]	I	2	20,22	1/1	100%	150 × 5	PO 90 × 5	VCR BEV
Bagatell et al. (PBC 2014) [28]	I	7	Uk (<21)	0/1	14%	100–150 × 5	PO 50–90 × 5	TMS
Kurucu et al. (Ped Hem Onc 2015) [29]	R	20	14 (1–18)	uk	55%	100 × 5	IV 20 × 5 × 2	None
Anderson et al. (Exp Opin Investig Drugs 2008) [30]	R	25	15 (uk)	7/9	64%	100 × 5	IV 10 × 5 × 2	None

R: retrospective; I: Phase I; IV: intravenous; PO: per os; TMZ: temozolomide; VCR: vincristine; BEV: bevacizumab; TMS: temsirolimus; uk: unknown; na: not applicable; PBC: Pediatric Blood and Cancer: An Ped: Annals of Pediatrics; Ped Hem Onc: Pediatric Hematology and Oncology.

and the Royal Marsden Hospital/Institute of Cancer Research, London, UK.

All patients/legal tutors included in the study signed informed consent for treatment and privacy according to the requirements of each individual institution.

The analysis period was set from March 2010 to April 2016.

Patients with the following characteristics were included: (1) diagnosis of EWS, (2) recurrent disease or disease progressing on frontline treatment, not amenable to surgical excision, (3) treatment with TEMIRI, (4) availability of demographic, clinical and follow-up data, (5) measurable disease as per RECIST 1.1 (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]) and (6) available radiological images for review.

The diagnosis was confirmed in all cases by an experienced sarcoma pathologist. Drugs were administered as follows: temozolomide 100 mg/m^2/day oral, days 1–5 and irinotecan 40 mg/m^2/day intravenous, days 1–5, every 21 days. Gastrointestinal toxicity prophylaxis with oral cefixime 400 mg/day, days 1–10, was recommended in all patients.

Patient characteristics including age, gender, ECOG performance status, LDH, primary tumor site, pattern of metastases, number of prior line of treatments, response to therapy, toxicity, date of progression, date of last follow-up or death were obtained from the databases or the patient clinical chart and collected in a study-specific case report form.

Response was assessed using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [31]. Patients were assessed for response after the first two cycles and, in case of response or stable disease, every two or three following courses of therapy. Response was assessed according to RECIST 1.1. Objective response was given by complete response [CR] + partial response [PR] and overall response rate (ORR) was calculated as the proportion of patients achieving either CR or PR. Disease control rate (DCR) was the duration of CR, PR and SD.

Patients undergoing surgery or radiotherapy with curative intent and achieving a complete remission of all sites of disease were classified as patients in disease-free status (DFS). Toxicity data were collected from clinical chart and from 'patient-toxicity' questionnaires, in some of the centers. Toxicity was graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4. In case of grade 4, neutropenia prophylactic use of G-CSF was allowed; therapeutic use of G-CSF was mandatory in case of febrile neutropenia.

Treatment was discontinued at progression or unacceptable toxicity. All patients who received at least one cycle were included in an intention-to-treat analysis.

Progression-free survival (PFS) and overall survival (OS) were estimated according to the Kaplan and Meier method with their respective 95% confidence intervals (CI) and calculated from the first day of TEMIRI administration to tumor progression or death or last follow-up visit, respectively.

Results

Fifty-one patients were identified. The median age was 21 years (range: 3–65 years). Seventeen patients (34%) were ≤18 years, and 34 (66%) were in the adult age range (i.e., >18 years of age). Seventeen patients (33%) were female and 34 (77%) were male. Twenty-six (52%) patients had an ECOG 0, 20 patients (40%) ECOG 1 and four patients (8%) had an ECOG 2. The clinical characteristics are displayed in Table 2.

Thirty-five patients (69%) had multiple sites of metastatic disease (with additional bone marrow involvement in 2), 11 patients (22%) had lung only disease and five (9%) had bone and local recurrence.

All patients were pretreated: 13 patients (25%), relapsing after adjuvant chemotherapy, received TEMIRI as first line therapy for recurrent/primary refractory disease, and 38 patients (75%) received this schedule as ≥2nd line therapy (25 patients as 2nd line, nine as 3rd line, four as 4th line of treatment). Fourteen (27%) patients had previously been treated with busulfan and melphalan (BuMel) with peripheral blood stem cell rescue (PBSC).

The median number of cycles was 5 (range: 1–31 cycles), with one patient with bone, lung, adrenal and soft tissue involvement, receiving up to 31 cycles as fourth line chemotherapy, achieving a 24 months SD and eventually undergoing CNS progression.

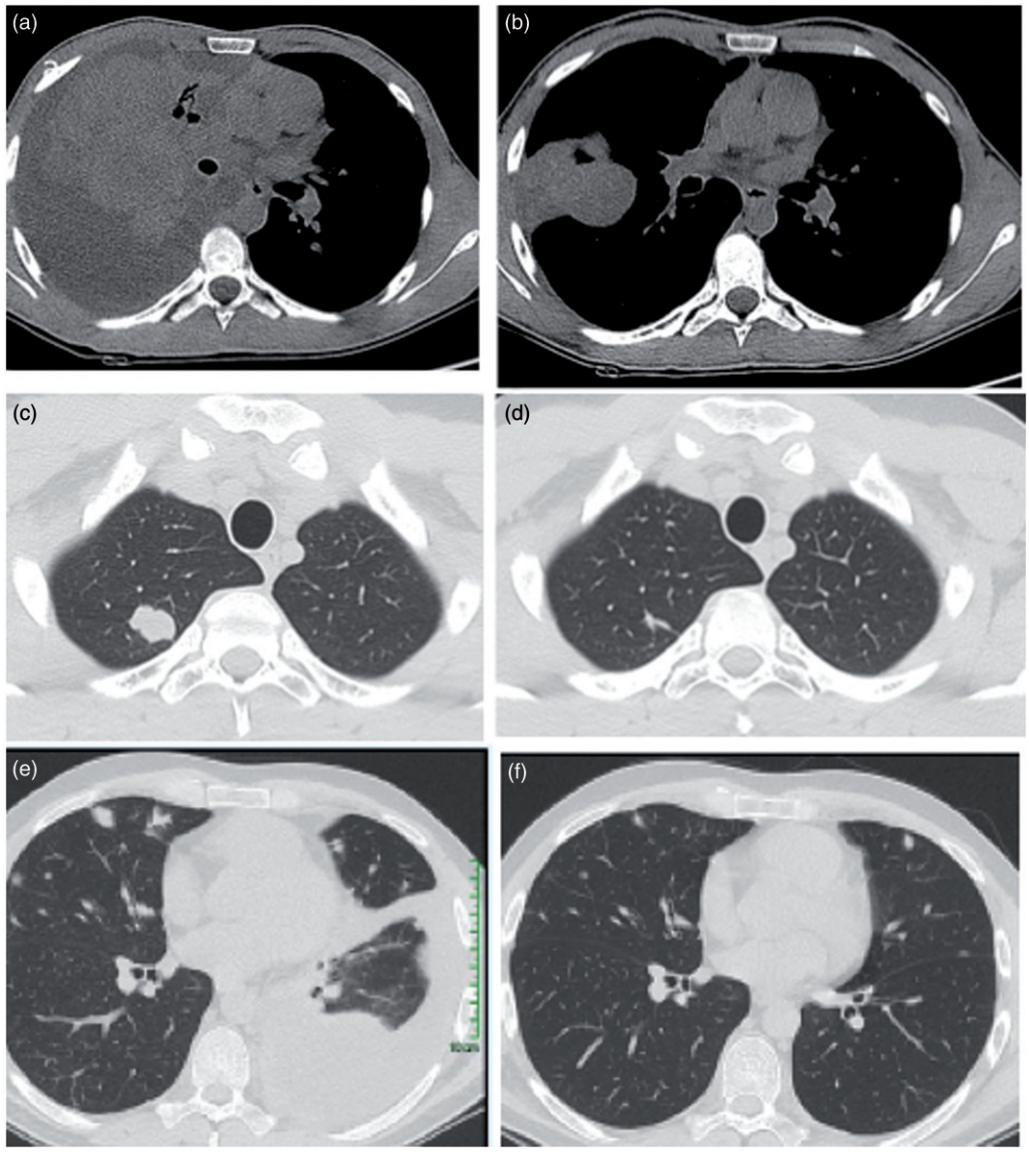

Figure 1. Massive pleural effusion and lung metastases before (a) and (b) after two cycles of chemotherapy with temozolomide and irinotecan; lung apical nodule before (c) and after (d) treatment; bilateral lung metastases and lower lung lobe pleura effusion before (e) and (f) after chemotherapy.

The response rate was 34% (CR 5 [10%], PR 12 [24%]) with LDH ($p = .004$) and ECOG ($p = .004$) predicting for response (Figure 1, Table 3). There was no significant difference in ORR according to age (Table 3).

Ten patients became disease-free (DFS cohort): five patients achieved CR with TEMIRI only (in two of them radiation therapy was added); five patients, in SD or PR with TEMIRI, DFS was achieved adding surgery (in three), radiation therapy (in one) or both (one).

The 6-months PFS was 49% (95% CI 35–63) and the median PFS was 3.9 months (range: 1–29 months) (Figure 2).

There was a significant difference in 6-month PFS according to ECOG (ECOG 0 6-months PFS 64% vs. ECOG 1 6-months PFS 40% vs. ECOG 2 6-months PFS 0 $p = .0002$) and LDH (LDH normal 6-months PFS 62% vs. LDH high 6-months PFS 22%, $p = .02$), whereas no significant differences were found according to age, sex, metastatic pattern, prior use of BuMel or line of treatment (Table 4).

One-year overall survival rate was 55% (95% CI 39–70). One-year OS was significantly better for responders: 84% for patients achieving an objective response (CR/PR), 64% for those with SD and 9% for those with PD, $p = .0001$ (Figure 2, Table 5).

Other factors associated with increased survival were ECOG 0 (ECOG 0 1-year OS 81% vs. ECOG $\geq$1 1-year OS 26%, $p = .001$), normal LDH level at TEMIRI treatment start (LDH normal 1-year OS 67% vs. LDH high 1-year OS 28%, $p = .04$), and patients achieving DFS after TEMIRI (DFS yes 1-year OS 100% vs DFS no 1-year OS 45%, $p = .02$) (Table 5).

After multivariate analysis, ECOG 0 ($p = .0002$) and LDH ($p = .01$) were confirmed as factors independently associate with OS (Table 6).

TEMIRI re-challenge

Two patients underwent TEMIRI re-challenge. One patient, with a metastatic spine sarcoma, achieved a CR after four

Table 2. Clinical characteristics of 51 patients with metastatic Ewing sarcoma (EWS).

	n (%)
Sex	
Female	17 (33)
Male	34 (77)
ECOG[a]	
0	26 (52)
≥1	24 (48)
Age	
≤14 years	8 (16)
15–17 years	9 (18)
≥18 years	34 (66)
LDH[b]	
High	19 (39%)
Normal	30 (61%)
Metastatic pattern	
Multiple sites[c]	35 (69%)
Lung	11 (22%)
Bone or LR	5 (9%)
Chemo lines at TEMIRI	
1[d]	13 (25%)
≥2	38 (75%)
Previous HCT (BuMel)	
Yes	14 (27%)
No	37 (73%)

LR: local recurrence; HCT (BuMel): high dose chemotherapy with busulphan and melphalan.
[a]Not available in one patient.
[b]Non-available in two patients.
[c]Including bone marrow involvement in two patients.
[d]1st line in ES patients progressing/relapsing after adjuvant standard chemotherapy.

Table 3. Analysis of response rate (RR) by clinical variable (total = 51).

	CR + PR (%)	SD (%)	PD (%)	
Age				
<18 years	3 (18)	10 (59)	4 (23)	.1
≥18 years	14 (41)	9 (27)	11 (32)	
Sex				
Male	11 (32)	15 (44)	8 (24)	.3
Female	6 (35)	4 (24)	7 (41)	
Pre BuMel				
Yes	4 (29)	7 (50)	3 (21)	.5
No	13 (36)	12 (32)	12 (32)	
Pattern of metastases at study entry				
Multiple sites	9 (26)	12 (34)	14 (40)	.1
Lung	5 (45)	5 (45)	1 (10)	
LR or bone	3 (60)	2 (40)	0	
LDH				
High	4 (21)	4 (21)	11 (58)	.004
Normal	11 (37)	15 (50)	4 (13)	
Lines at TEMIRI				
1	5 (39)	4 (31)	4 (31)	.8
≥2	12 (32)	15 (39)	11 (29)	
ECOG				
0	8 (31)	15 (58)	3 (11)	.004
1–2	9 (37)	4 (17)	11 (46)	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

cycles and TEMIRI was withdrawn after 10 cycles. Due to disease progression at 5 months off-therapy, he underwent TEMIRI re-challenge achieving a PR (ongoing after 15 cycles at last follow up). The second patient, also with lung metastases, achieved a CR after six cycles on TEMIRI, and underwent total lung irradiation. After 6 months he had a PD and was re-challenged with TEMIRI, achieving a PR lasting 22 cycles.

Toxicity

The median number of TEMIRI cycles was 5 (range 1–31 cycles). Grade 3 and 4 toxicity included neutropenia in six patients (12%), thrombocytopenia in two (4%) and diarrhea in two (4%) patients (Table 7), with none of patients with $a > 10\%$ weight loss. Nine patients (18%) had delayed treatment, while in one patient dose reduction by 33% of the scheduled doses was necessary due to combined grade 3–4 thrombocytopenia and neutropenia after the first cycle. Growth factors were needed in four patients, two patients required hospitalization (one for diarrhea and fever, one for G4 thrombocytopenia requiring transfusions). Overall grade 3 and 4 was reported in 10/51 (20%) adult patients and in 7/10 (70%) pediatric cases, with median age for patients with toxicity (17 years, range 3–65), inferior to that of patients with no toxicity (25 years, range 3–50).

Discussion

Treatment options for recurrent EWS and for disease progressing during frontline therapy include various chemotherapy schedules [13,16,18–21], but the optimal sequence of drugs remains to be defined. Prognostic factors at first recurrence associated with higher post-relapse survival are: the interval from initial diagnosis to recurrence (better if more than 2 years), disease sites at recurrence (worse if combined bone and lung), serum LDH (worse if high) and the treatment outcome [5–9]. Predictive factors for response to chemotherapy are still to be identified. TEMIRI has been studied in retrospective studies mainly including pediatric patients [13,22–30] however, none of these studies have reported on putative predictive markers of response and PFS. Only one study has been published with single agent temozolomide [11] while different schedules of single agent irinotecan are reported in different trials [14,32,33]. Protracted irinotecan infusion was shown to increase number of cells in S-phase exposed to the drug [34]. The addition of temozolomide, through DNA methylation, seems to cause localization and enhancement of topoisomerase I cleavage complex allowing irinotecan to more effectively stabilize the DNA–enzyme complex [35]. Preclinical studies suggest that antitumor activity of the combination of temozolomide and irinotecan is only partially dependent of O6-methylguanine-DNA methyltransferase and mismatch repair phenotypes in xenograft models [36]. The two drugs hold different toxicities profiles and different mechanism of resistance. In addition, the introduction of third generation cephalosporin has resulted in a reduction of the incidence of diarrhea, the major dose limiting toxicity of the regimen [37].

The major limitation of the present series is its retrospective design, which might affect the uniformity of toxicity and response assessment.

Nonetheless, our multicenter study is the largest study on the combination of irinotecan and temozolomide in recurrent and primary refractory EWS, and confirms that this combination is active in both adult and pediatric patients. Among 51 treated patients five achieved a complete response and 12 partial responses. It is important to note the relation

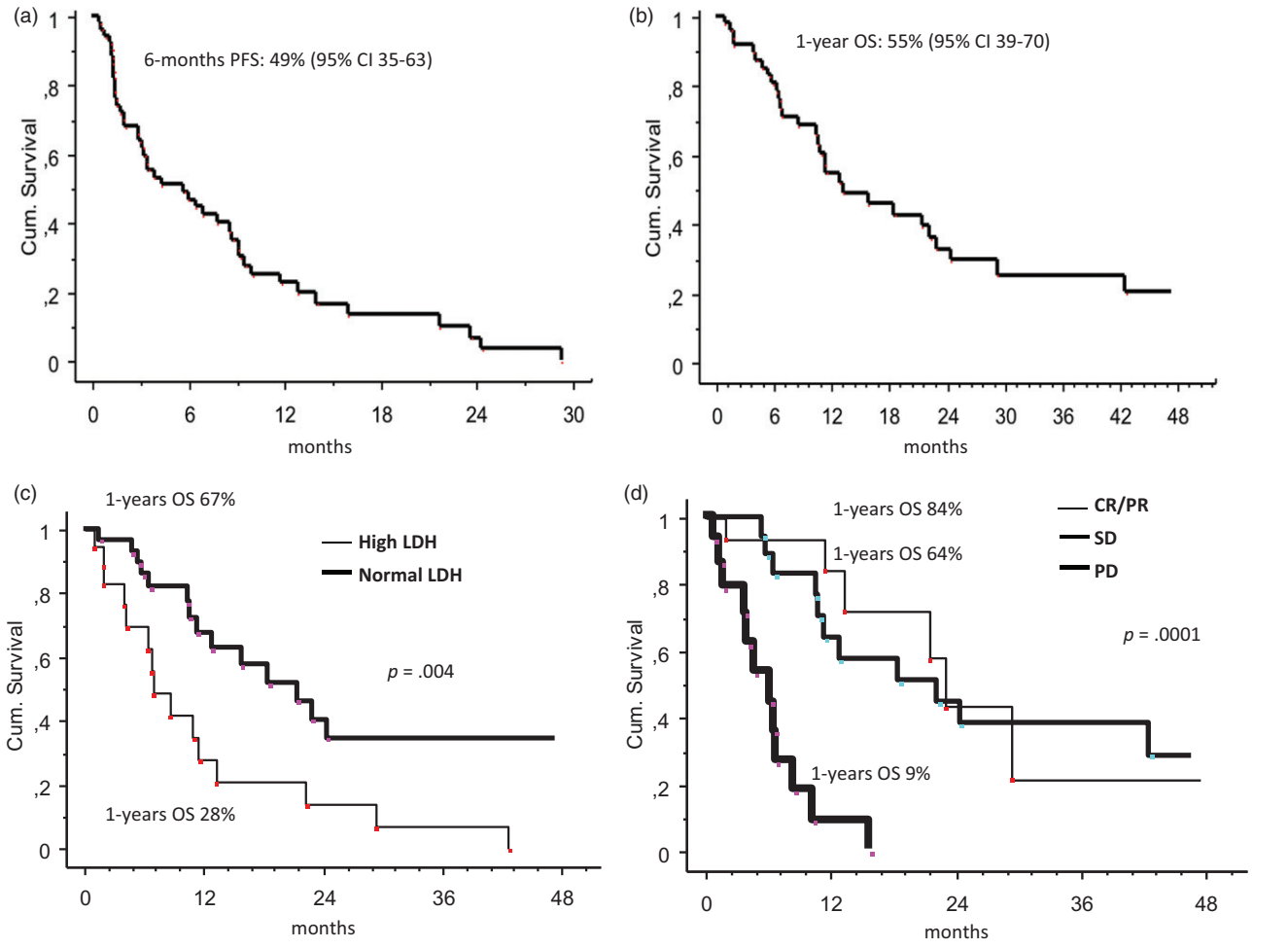

Figure 2. Outcome of adult and pediatric Ewing sarcoma patients treated with TEMIRI: (a) 6-months progression-free survival (PFS); (b) 1-year overall survival (OS); (c) 1-year OS according to LDH levels before TEMIRI treatment; (d) 1-year OS according to radiological response (RECIST 1.1).

Table 4. Univariate analysis for progression-free survival (PFS).

	Pts no.	% 6-months PFS	95% CI	*p*
Overall	51	49	35–63	
Age				
<18 years	9	44	12–77	.9
≥18 years	42	55	34–66	
Sex				
Female	17	43	19–68	.9
Male	34	42	35–69	
Metastatic pattern				
Lung	11	81	57–100	.3
Bone + Loc Rec	5	60	17–100	
Multiple sites	35	38	21–54	
ECOG				
0	26	64	45–83	.006
≥1	24	34	14–54	
Chemo Line at TEMIRI				
1	13	46	19–73	.8
≥2	38	50	33–66	
LDH				
High	19	22	3–42	.02
Normal	30	62	44–79	

Pts: patients.

observed between ORR and PFS in our population. In adult patients, the ORR was higher compared to that of younger patients, but this did not translate in a superior probability of PFS that was not significantly different between adults and pediatric patients.

Table 5. Univariate analysis for overall survival (OS).

	Pts no.	% 1-year OS	95% CI	*p*
Overall	51	55	39–70	
Age				
<18 years	17	49	19–78	.7
≥18 years	34	57	39–75	
Sex				
Female	17	48	20–76	.2
Male	34	62	44–80	
Metastatic pattern				
Lung	11	100		.08
Bone + Loc Rec	5	80	45–100	
Multiple sites	35	38	20–56	
ECOG				
0	26	81	64–98	.0001
≥1	24	26	5–47	
Chemo Line at TEMIRI				
1	13	81	56–100	.3
≥2	38	49	32–66	
LDH				
High	19	28	5–51	.04
Normal	30	67	48–86	
RECIST response				
CR/PR	17	84	64–100	.0001
SD	19	64	40–97	
PD	15	9	0–25	
DFS				
Yes	10	100		.02
No	41	45	28–62	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; DFS: disease free status; progressive disease.

Table 6. Multivariate analysis for overall survival (OS).

Variable	RR	*p*
LDH		
Normal	1	.9
High	0.9	
ECOG		
≥1	1	.0002
0	0.08	
RECIST response		
SD	1	.001
CR/PR	0.2	
PD	5.6	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RR: response rate.

Table 7. Grade 3–4 toxicity and compliance.

	N	%
Diarrhea	2	4
Neutropeni	6	12
Thrombocytopenia	2	4
Nausea/vomiting	1	2
γ-GT level	1	2
Pts with TEMIRI delays	9	18
Pts with TEMIRI dose reduction due to diarrhea	1	2

Pts: patients.

At the same time it is important to underline that prolonged disease stabilization was reported with an adult patient that was on treatment for more than 30 cycles of TEMIRI.

On univariate analysis, the only two factors predictive for response to TEMIRI in terms of PFS were ECOG and LDH, but not the number of chemotherapy lines. This suggests that TEMIRI can potentially be safely used in patients who have already received more than one line for recurrent/progressive disease, maintaining the goal of achieving a new response if the performance status is still good and LDH in the normal range.

The survival analysis confirmed the importance of ECOG and LDH and also demonstrated an association with OS and response: in particular similar outcome was demonstrated for patients achieving PR/CR and for those with a disease stabilization, while patients progressing on TEMIRI represent a subgroup with a very poor outcome. This study suggested that, whenever possible, surgery and radiotherapy to all sites of metastases should be performed, with all patients attaining a disease remission (DFS group) in this series are alive at 1 year. Also, TEMIRI re-challenge might represent a therapeutic option for those patients relapsing after TEMIRI interruption, in case of disease complete remission.

The schedule we used, with 40 mg/m^2/die Irinotecan for 5 days, is manageable comparing the ones at lower dose [10–20 mg/m^2/die for 5 days] for 2 weeks in the first pediatric studies [38]. We observed less gastrointestinal toxicity than previously reported in other studies [13]. Since temozolomide has no overlapping toxicity with irinotecan, the hematological toxicities are quite similar to those ones observed with monotherapy [13].

In conclusion, our study confirms the efficacy and safety of temozolomide and irinotecan in recurrent/refractory Ewing's sarcoma in both the pediatric and adult population and provides a benchmark for further studies.

In addition, our data indicate that irinotecan and temozolomide should be considered as a control arm for future randomized trials in relapsed EWS. The results of the randomized trial rEECur, presently ongoing (http://www.euroewing.eu/clinical-trials/reecur/reecur-update) [39] comparing TEMIRI with three other regimens adopted in patients with recurrent EWS, will define the best treatment sequence. The activity and toxicity profile of TEMIRI suggest that this combination might be added to conventional chemotherapy combinations in the first-line therapy setting.

Disclosure statement

No potential conflict of interest was reported by the authors.

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