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Original Research

Outcome of SIOP patients with low- or intermediate-risk Wilms tumour relapsing after initial vincristine and actinomycin-D therapy only – the SIOP 93–01 and 2001 protocols

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Abstract ***Purpose:*** Society of International Pediatric Oncology – Renal Tumor Study Group (SIOP-RTSG) treatment recommendations for relapsed Wilms tumour (WT) are stratified by the intensity of first-line treatment. To explore the evidence for the treatment of patients relapsing after vincristine and actinomycin-D (VA) treatment for primary WT, we retrospectively evaluated rescue treatment and survival of this patient group.
Patients and methods: We included 109 patients with relapse after VA therapy (no radiotherapy) for stage I-II primary low- or intermediate-risk WT from the SIOP 93–01 and SIOP 2001 studies. Univariate Cox regression analysis was performed to study the effect of relapse treatment intensity on event-free survival (EFS) and overall survival (OS). Relapse treatment intensity was classified into vincristine, actinomycin-D, and either doxorubicin or epirubicin (VAD), and more intensive therapies (ifosfamide/carboplatin/etoposide [ICE]/≥ 4 drugs/high-dose chemotherapy with haematopoietic stem cell transplantation [HD HSCT]).
Results: Relapse treatment regimens included either VAD, or cyclophosphamide/carboplatin/etoposide/doxorubicin (CyCED), or ICE backbones. Radiotherapy was administered in 62 patients and HD HSCT in 15 patients. Overall, 5-year EFS and OS after relapse were 72.3% (95% confidence interval [CI]: 64.0–81.6%) and 79.3% (95% CI: 71.5–88.0%), respectively. Patients treated with VAD did not fare worse when compared with patients treated with more intensive therapies (hazard ratio EFS: 0.611 [95% CI: 0.228–1.638] [*p*-value = 0.327] and hazard ratio OS: 0.438 [95% CI: 0.126–1.700] [*p*-value = 0.193]).
Conclusion: Patients with relapsed WT after initial VA-only treatment showed no inferior EFS and OS when treated with VAD regimens compared with more intensive rescue regimens. A subset of patients relapsing after VA may benefit from less intensive rescue treatment than ICE/CyCED-based regimens and deserve to be pinpointed by identifying additional (molecular) prognostic factors in future studies.

1. Introduction

Overall survival (OS) of patients with Wilms tumour (WT) has improved to more than 90% for localised disease [1,2]. Still, approximately 5%, 12% and 25% of WT patients with low-risk (LR), intermediate-risk (IR) and high-risk (HR) histology tumours, suffer from relapse [3,4]. Survival after relapse ranges between 55% and 80% for patients with local non-anaplastic primary WT, depending mainly on the stage and histology of primary disease and therefore also on the corresponding intensity of first-line treatment [4–7].

The UMBRELLA International Society of Pediatric Oncology – Renal Tumor Study Group (SIOP-RTSG) protocol stratifies patients with relapsed WT primarily on the extent of their first-line treatment and recognises patients treated with only vincristine and/or actinomycin-D (VA) and without radiotherapy as standard-risk relapse patients (Supplementary Table 1) [1]. Although the risk of relapse after VA-only treatment is relatively low, patients with such upfront therapy constitute a relatively large group, contributing more than one-third of all relapses.

For VA-treated patients who subsequently relapse, the UMBRELLA protocol recommends a four-drug treatment, that is, alternating cyclophosphamide, doxorubicin and carboplatin, etoposide (CyCED), usually combined with surgery and/or radiotherapy. This recommendation is based on two non-randomised studies (National Wilms Tumor Study Group's [NWTSG] NWTS-5 [6], and United Kingdom relapsed WT trial [UKWR] [8]), which suggested improved

survival of standard-risk relapse patients after treatment with VCyED (vincristine, cyclophosphamide, etoposide, doxorubicin) and CyED, respectively, when compared with historic controls treated without a uniform relapse protocol [9,10]. From these studies, the event-free survival (EFS) of standard-risk relapse patients treated with CyCED is expected to be 70–80% [6]. However, the upfront treatment for primary WT during the NWTS-5 and for the patients registered on the UKWR was immediate nephrectomy, and the benefit of a CyCED-based rescue treatment over a three-drug regimen (VA and doxorubicin or epirubicin) has never been evaluated in relapsed patients treated according to SIOP regimens that advocate preoperative chemotherapy.

Therefore, this retrospective study aimed to seek further evidence for the use of CyCED therapy in SIOP standard-risk relapse WT patients. Accordingly, all relapsed VA-treated patients registered in the SIOP-RTSG 93–01 and 2001 studies were identified and patient outcome, stratified by relapse regimen, was assessed.

2. Patients and methods

2.1. Patients

Patients who relapsed after first-line treatment with vincristine and/or actinomycin-D only (no radiotherapy) according to SIOP 93–01 or SIOP 2001 protocol and who were registered in the SIOP-RTSG dataset between October 1993 and September 2012 were included. Patients who were recommended VA-only according to the protocols are patients with stage I LR/IR tumours (93–01) and stage I/II LR, stage I/II IR, and stage III LR disease (2001) (Table 1) [11,12]. Patients with upfront stage III tumours, initially requiring radiotherapy, were excluded from the analyses. Exclusion also applied to tumours classified as stage II with positive lymph nodes during the 93–01 (treated as stage III tumours), which were reclassified as stage III according to the SIOP 2001 protocol [13,14]. All patients with high-risk primary WT according to SIOP 2001 classification, that is, all blastemal-type (BT) and diffuse anaplastic (DA) tumours (in SIOP 93–01 and SIOP 2001) were excluded. Reclassification of 93–01 BT WTs according to the SIOP 2001 classification had already been performed by the international SIOP pathology review panel, as reported previously [15].

To compare survival rates between patients treated with relapse regimens of different intensities, all reported therapies at relapse were identified. The SIOP 93–01 and 2001 protocols included general recommendations for relapse treatment, but limited stratification guidance (Supplementary Table 1). Proposed relapse regimens included etoposide, carboplatin, ifosfamide and epirubicin/doxorubicin (ECIE/ECID) during the 93-01 study, and either VAD, cyclophosphamide, carboplatin, etoposide and doxorubicin/vincristine (CyCED/CyCEV) or ifosfamide/cyclophosphamide, carboplatin and etoposide (ICE/CyCE) in the 2001 study. High-dose chemotherapy with subsequent haematopoietic stem cell transplant (HD HSCT) was not routinely recommended. Patients registered in the SIOP WT 2001 trial in the United Kingdom and Ireland were eligible to be entered into the UKWR national trial (until 2008). Patients who initially received VA only were treated with either VAD (stage I, non-anaplastic histology and relapse >6 months from diagnosis) or CyED (stage II, non-anaplastic histology and relapse >6 months).

The SIOP 93–01 registered 119 participating centres from 26 countries, and 251 centres from 26 countries participated in the SIOP 2001 [11,12]. The studies were approved by national ethical committees, the SIOP2001 study was submitted to the international trial register (EudraCT number SIOP 2001: 2007-004591-39), and

Table 1
Postoperative primary treatment in SIOP 93–01 and SIOP 2001.

Stage	SIOP 93-01			SIOP 2001		
	LR	IR (+BT)	HR (+FA/DA)	LR	IR (+FA)	HR (+BT/DA)
I	–	VA[a]	ECIE*	–	VA[b]	VAD
II	VAD or AVE*	VAD or AVE*	ECIE* + RT	VA	VA versus VAD[c]	CyCED + RT[d]
III	VAD or AVE* + RT	VAD or AVE* + RT	ECIE* + RT	VA	VA versus VAD[c] + RT	CyCED + RT

Abbreviations: A, actinomycin-D; BT, blastemal-type; C, carboplatin; Cy, cyclophosphamide; D, doxorubicin; DA, diffuse anaplasia; E, etoposide; E*, epirubicin; FA, focal anaplasia; HR, high-risk; I, ifosfamide; IR, intermediate-risk; L, low-risk; RT, radiotherapy.

[a] Including stage I anaplasia (FA and DA).

[b] Gesellschaft für pädiatrische Onkologie und Hämatologie (GPOH) treated all non-stromal, non-epithelial intermediate risk tumours with a preoperative volume of >500 mL with VAD.

[c] GPOH treated non-stromal, non-epithelial intermediate risk tumours with a preoperative volume of >500 mL according to the HR protocol.

[d] BT tumours were not treated with RT.

the patients were registered upon signed informed consent. National coordinators and local centres were contacted to obtain missing data on treatment regimens at relapse.

3. Methods

We classified the intensity of relapse treatments into 'VAD' (which includes either doxorubicin or epirubicin as anthracycline) and 'more intensive' relapse therapies (including patients treated with ICE, regimens with ≥4 drugs, and all regimens including HD HSCT). Survival rates were compared between these groups. In a secondary analysis among the more intensively treated patients, survival after treatment with ifosfamide-based versus cyclophosphamide-based regimens was compared. For this analysis, three-drug cyclophosphamide-based regimens (e.g. the UKWR CyED arm) were included in addition to ≥4-drug regimens. Also the contribution of HD HSCT was explored in the group of intensively treated patients. Finally, to identify those who benefitted most from VAD treatment, clinical characteristics of VAD-treated patients were compared between those who did and did not present with an event/succumbed after the first recurrence.

4. Statistical analysis

We estimated 5-year EFS and OS rates after relapse using Kaplan–Meier analysis, and log-rank analysis was performed to compare survival rates between treatment groups. Events were defined as progressive disease despite upfront relapse treatment (within 6 months after the start of therapy), second relapse and all causes of death for EFS, and all causes of death for OS. Associations between clinical variables were studied using Fisher's exact test for categorical variables. To determine the effect of the different chemotherapeutic relapse treatment regimens on EFS and OS rates, univariate Cox regression analyses were performed with the following variables: study (SIOP 93–01 versus SIOP 2001), sex, age at diagnosis (<24, 24–48, 49–96, >96 months), stage of the primary tumour, age at relapse, pattern of relapse (local versus metastatic/combined [local and metastatic]), time to relapse (<6 months versus ≥6 months from primary diagnosis), and therapy at relapse. To determine which clinical characteristics were associated with the administered chemotherapy (VAD versus more intensive therapy), a logistic regression model was fitted. The variables considered for the logistic regression model included those used in univariate Cox regression analysis. Pearson's correlation test evaluated correlations between the variables. Forward selection, backward elimination and bidirectional elimination analyses were performed, and the optimal model was selected based on the Akaike information criterion. The model fit was determined using the McFadden's pseudo R^2 value, with values above 0.2 representing a good fit. *P* values of <0.05 were considered statistically significant. Statistics were performed using R-4.0.2 (R Core Team [2020]), and the survival (v. 3.1–12 Therneau T [2020]) and survminer (v. 0.4.8 Kassambara A *et al.* [2020]) packages.

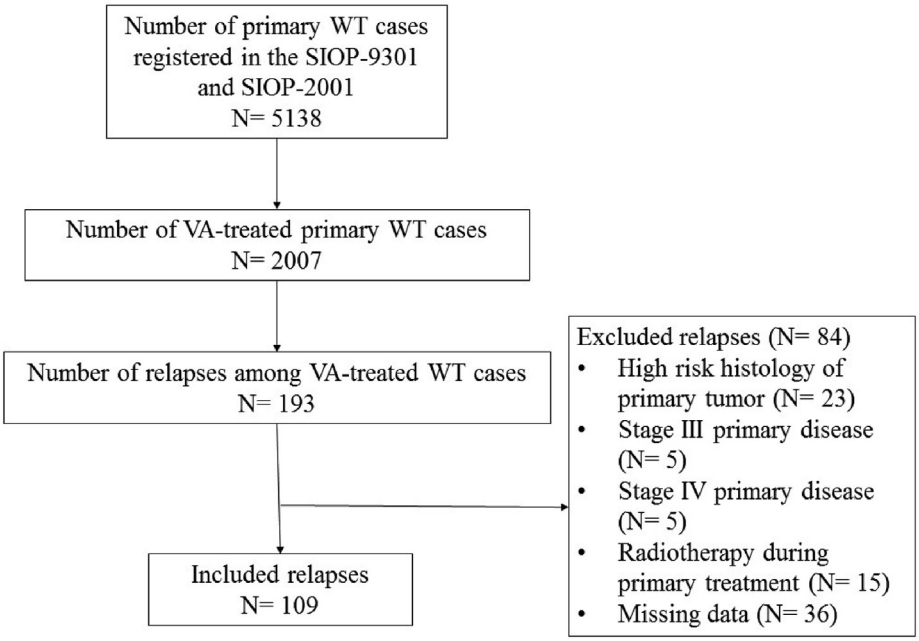

Fig. 1. Flow diagram of included and excluded Wilms tumour (WT) cases from a total of 5138 primary unilateral WT patients registered in the SIOP 93–01 and the SIOP 2001 studies. N = number of patients.

Table 2
Patient characteristics per study (SIOP 93–01 and SIOP 2001).

Characteristics	SIOP 93-01	SIOP 2001	Total
Number of study patients	33	76	109
Sex			
• Male	13 (39.4%)	42 (55.3%)	55 (50.5%)
• Female	20 (60.6%)	34 (44.7%)	54 (49.5%)
Characteristics at primary diagnosis			
Age at primary diagnosis (months)			
• <24	9 (27.3%)	16 (21.1%)	25 (22.9%)
• 24–48	12 (36.4%)	20 (26.3%)	32 (29.4%)
• 49–96	12 (36.4%)	35 (46.1%)	47 (43.1%)
• >96	0 (0.0%)	5 (6.6%)	5 (4.6%)
Tumour stage			
• I	27 (81.8%)	63 (82.9%)	90 (82.6%)
• II	6 (18.2%)	13 (17.1%)	19 (17.4%)
Characteristics at relapse			
Age at relapse (months)			
• <24	4 (12.1%)	5 (6.6%)	9 (8.3%)
• 24–48	9 (27.3%)	19 (25.0%)	28 (25.7%)
• 49–96	19 (57.6%)	39 (51.3%)	58 (53.2%)
• >96	1 (3.0%)	13 (17.1%)	14 (12.8%)
Pattern of relapse			
• Local	7 (21.2%)	21 (27.6%)	28 (25.7%)
• Metastatic	22 (66.7%)	47 (61.8%)	69 (63.3%)
• Combined	4 (12.1%)	8 (10.5%)	12 (11.0%)
Time to relapse from primary diagnosis			
• <6 months	6 (18.2%)	8 (10.5%)	14 (12.8)
• ≥6 months	27 (81.8%)	68 (89.5%)	95 (87.2%)
Therapy at relapse			
Chemotherapy			
• VAD	5	21	26
• More intensive regimens[a]	24	42	66
o Ifosfamide-based	*19/24*	*9/42*	*28/66*
ICE-based	*- 18/19*	*- 9/9*	*- 27/28*
o *Ifosfamide + cyclophosphamide-based*	*1/24*	*7/24*	*8/66*
ICE-based	*- 0/1*	*- 7/7*	*- 7/8*
o Cyclophosphamide-based	*2/24*	*23/42*	*25/66*
o Other intensive therapy	*2/24*	*3/42*	*5/66*
• Other regimens[b]	4	13	17
o *Cyclophosphamide-based*[c]	*0/4*	*7/13*	*7/17*
Radiotherapy			
• No	14	29	43
• Yes	15	45	60
• Unknown	4	2	6
HD HSCT			
• No	28	66	94
• Yes	5	10	15

Abbreviations: HD HSCT, high-dose chemotherapy with haematopoietic stem cell transplantation.

[a] See Supplementary Table 3 for an extensive overview of the administered treatment regimens.

[b] Other regimens include those that were not VAD and were not considered more intensive (Supplementary Table 3).

[c] Cyclophosphamide, cisplatin and etoposide (CyCE) and cyclophosphamide, doxorubicin and etoposide (CyDE) regimens were included in the cyclophosphamide-based treatment group (N = 32 in total).

5. Results

The SIOP database registered 5138 patients with unilateral WT in the SIOP 93–01 and the SIOP 2001 study. From the total cohort, 2007 (39.1%) patients were treated with VA-only, and 193 (9.6%) of these patients experienced tumour relapse, predominantly within 5 years after primary diagnosis. This cohort comprised 27.3% of all relapses. Of the 193 cases, we excluded 48 patients (24.9%; Fig. 1). Details on relapse treatment were missing in 36 (24.8%) of the remaining 145 patients. Thus, a total of 109 patients were evaluable (Fig. 1).

Patient characteristics per study are presented in Table 2. Most patients (N = 107) had a WT with IR histology, and two presented with completely necrotic, LR WT. The 36 patients with missing data presented with similar characteristics, except for relapse location, which was more often local in our cohort (Supplementary Table 2).

In total, 36 different chemotherapeutic relapse regimens were reported (Supplementary Table 3). VAD was administered to 26 patients, whereas 66 patients received more intensive treatment (15/66 patients additionally received HD HSCT). The remaining 17 patients received regimens that were not VAD, nor considered more intensive. Among patients with known data on local therapy at relapse, 60 of 103 were treated with radiotherapy and 77 of 105 were treated with surgery. Among the 43 patients who had not been treated with radiotherapy, 32 had undergone surgery at relapse. The extent of surgery and response to local therapy, however, were unknown.

5.1. Outcome of all relapsed WT patients initially treated with VA

The estimated 5-year EFS rate post-relapse in the total cohort was 72.3% (95% confidence interval [CI]: 64.0–81.6%) and estimated 5-year OS was 79.3% (95% CI: 71.5–88.0%; Fig. 2). The median follow-up time was 73 months (range: 8–160 months). All 21 deaths were disease related and not related to treatment toxicity.

Patients treated during the SIOP 93-01 study had inferior EFS and OS rates after relapse, with an almost 3-fold increase in the risk of event and death when compared with patients treated according to the SIOP 2001 protocol. Other characteristics at primary diagnosis and at relapse, excluding relapse treatment, were not significantly associated with survival (Table 3).

5.2. Outcome according to relapse treatment

The clinical characteristics of patients treated with VAD were comparable to those of patients treated with more intensive therapy (Supplementary Table 4). Five-year EFS and OS rates after VAD therapy compared with

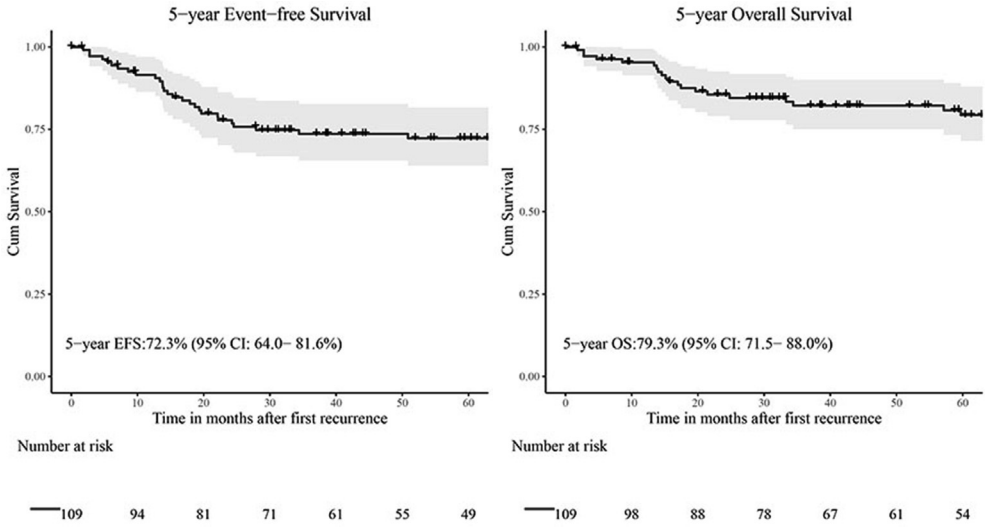

Fig. 2. Kaplan–Meier curves showing 5-year event-free survival estimate (EFS) with 95% confidence interval (CI) (left) and 5-year overall survival estimate (OS) with 95% CI (right) after first recurrence.

more intensive treatment were not significantly different (Tables 3 and 4). Similarly, we observed no survival difference between patients treated with VAD and ICE-based regimens. ICE-based regimens were more often administered during the 93-01 study (p-value = 0.015; Supplementary Table 5).

In a subgroup analysis, the 5-year EFS and 5-year OS rates were comparable between patients treated with cyclophosphamide-based and ifosfamide-based regimens (Table 4). Ifosfamide-based regimens were more often administered during the 93-01 study (p-value $\leq$0.001; Supplementary Table 6). The 5-year EFS and OS rates for patients treated with ifosfamide *and* cyclophosphamide did not differ significantly between patients treated with ifosfamide-based or cyclophosphamide-based regimens only (p-value EFS = 0.734 and p-value OS = 0.945 [log rank (overall pooled)]).

To determine which clinical characteristics were associated with the administered chemotherapy, a logistic regression model was fitted with VAD and intensive therapy as dependent variables. The resulting model, including sex and time to relapse as independent variables (Supplementary Table 7), did not adequately fit the data (McFadden's pseudo R^2: 0.054). This illustrates that none of the known clinical factors was significantly associated with administered treatment.

The estimated 5-year EFS rates were comparable between the selected group of patients treated with and without HD HSCT (hazard ratio: 1.787 [95% CI: 0.678–4.708] [p-value = 0.240]; Table 4).

Treatment with HD HSCT was associated with a 5-year OS of 51.9% (95% CI: 30.3–89.1%), whereas patients who had not received HD HSCT had a 5-year OS rate of 82.0% (95% CI: 71.2–94.4%; hazard ratio: 2.8894 [95% CI: 1.003–8.354] [p-value = 0.049]). Clinical characteristics did not differ significantly between patients treated with and without HD HSCT (Supplementary Table 8).

We finally aimed to explore which patients benefitted most from VAD therapy. The clinical characteristics were not significantly different between patients who did and did not present with a second event, nor between patients who died and who were still alive at last follow-up (Supplementary Tables 9 and 10). The 5-year EFS rate in the group of patients treated with VAD was 80.0% (95% CI: 65.8–97.3%), and the 5-year OS rate was 88.0% (95% CI: 76.1–100%).

6. Discussion

We aimed to seek further evidence for the use of CyCED therapy in patients who relapsed after VA-only therapy and were registered in the SIOP-RTSG 93–01 and 2001 studies. Based on the relapse recommendations in the study protocols, we expected that most patients in our cohort had received either VAD, CyCED or ICE/ECIE/ECID. In reality, a large variety of regimens had been prescribed. This reflects the uncertainty when assigning rescue treatment based on the current weak evidence.

Survival rates after VAD compared with more intensive therapies, including CyCED, were not different. However, relapse treatment recommendations in the SIOP 93–01 and the SIOP 2001 protocols were limited, and the choice of therapy was predominantly based on the local paediatric oncology team (only the United Kingdom/Ireland had a national relapse protocol). Therefore, the extent of relapse therapy may have been dependent on other (unknown) clinical factors than upfront treatment and study protocol alone. This is in line with our logistic regression model for therapy choice, which suggested that none of the known clinical

Table 3
Univariate Cox regression analysis for EFS and OS after first recurrence.

Variable		Sample size		Events EFS	Hazard ratio EFS (95% CI)	*p*-value	Events OS	Hazard ratio OS (95% CI)	*p*-value
Total		109		28			21		
	Study	76	2001	13	1		9	1	
		33	93–01	15	2.818 (1.339–5.929)	**0.006**	12	2.927 (1.229–6.973)	**0.015**
	Sex	55	Male	13	1		11	1	
		54	Female	15	1.177 (0.560–2.473)	0.668	10	0.926 (0.393–2.182)	0.861
	Characteristics at primary diagnosis								
	Age at diagnosis (months)	25	<24	5	1	0.520	3	1	0.448
		32	24–48	11	2.011 (0.698–5.795)	0.196	9	2.719 (0.736–10.049)	0.134
		47	49–96	10	1.250 (0.427–3.657)	0.684	8	1.584 (0.420–5.973)	0.497
		5	>96	2	2.002 (0.388–10.330)	0.407	1	1.817 (0.188–17.554)	0.606
	Stage	90	I	24	1		17	1	
		19	II	4	0.831 (0.288–2.396)	0.732	4	1.184 (0.398–3.524)	0.762
	Characteristics at relapse								
	Age at relapse (months)	9	<24	1	1	0.620	1	1	0.764
		28	24–48	9	3.296 (0.417–26.020)	0.258	6	2.045 (0.246–16.995)	0.508
		58	49–96	13	2.436 (0.319–18.628)	0.391	10	1.805 (0.231–14.109)	0.573
		14	>96	5	3.466 (0.405–29.685)	0.257	4	2.920 (0.325–26.223)	0.339
	Pattern of relapse	28	Local	5	1		4	1	
		81	Metastatic/ combined	23	1.578 (0.600–4.151)	0.356	17	1.467 (0.493–4.359)	0.491
	Time to relapse (months)	95	≥6	24	1		17	1	
		14	<6	4	1.150 (0.399–3.316)	0.796	4	1.688 (0.567–5.023)	0.347
	Therapy at relapse								
	Chemotherapy	66	More intensive	19	1		15	1	
		26	VAD	5	0.611 (0.228–1.638)	0.327	3	0.438 (0.126–1.517)	0.193
		34	ICE-based[a]	7	1		5	1	
		26	VAD	5	0.894 (0.284–2.819)	0.849	3	0.709 (0.169–2.969)	0.637
	HD HSCT[b]	51	No	13	1		9	1	
		15	Yes	6	1.787 (0.678–4.708)	0.240	6	2.894 (1.003–8.354)	**0.049**
	Radiotherapy	43	No	13	1	0.081	9	1	0.603
		60	Yes	11	0.618 (0.277–1.379)	0.239	10	0.902 (0.363–2.238)	0.902
		6	Unknown	4	2.253 (0.733–6.919)	0.156	2	1.966 (0.420–9.202)	0.391

Statistically significant *p* values are represented in boldface.
Abbreviations: CI, confidence interval; EFS, event-free survival; HD HSCT, high-dose chemotherapy with haematopoietic stem cell transplantation; OS, overall survival.
[a] Subset of more intensively treated patients (Supplementary Table 3).
[b] Among intensively treated patients.

Table 4
Survival rates according to relapse treatment.

Relapse treatment[a]	N	5-year estimated EFS (95% CI)	5-year estimated OS (95% CI)
VAD	26	80.0% (65.8–97.3%)	88.0% (76.1–100%)
Intensive therapy	66	67.6% (56.4–80.9%)	75.2% (64.5–87.6%)
ICE-based therapy	34	77.0% (63.3–93.5%)	86.3% (74.5–99.9%)
Ifosfamide-based	28	69.4% (53.8–89.6%)	80.1% (65.8–97.5%)
Cyclophosphamide-based	32	74.8% (59.9–93.3%)	73.1% (55.7–95.8%)
Intensive therapy + HD HSCT	15	53.3% (31.7–89.7%)	51.9% (30.3–89.1%)
Intensive therapy – HD HSCT	51	71.5% (59.3–86.2%)	82.0% (71.2–94.4%)

Abbreviations: CI, confidence interval; EFS, event-free survival; HD HSCT, high-dose chemotherapy with haematopoietic stem cell transplantation; N, number of patients; OS, overall survival.
[a] Treatment groups include overlapping patients.

factors were significantly associated with administered treatment. Conceivably, the tumour burden at relapse (e.g. number of tumour foci and the tumour diameter at relapse [16]) may have influenced the choice of treatment. Unfortunately, data on the extent of the tumour at relapse, other than location, were not available.

We observed no survival benefit of patients treated with ICE-based regimens when compared with VAD therapy. The type of alkylating agent (i.e. ifosfamide or cyclophosphamide) used in more intensive treatment regimens did not affect survival rates. However, the independent value of ifosfamide-based regimens remains uncertain as this drug (alone and as part of ICE-based regimens) was more often administered during the SIOP 93–01. Treatment during the SIOP 93–01 rather than the 2001 study was associated with poorer survival. This

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urvival difference between the two SIOP studies may suggest that personalised management of relapsed WT has improved over the years, possibly reflecting improved risk stratification and subsequent treatment allocation during the SIOP 2001 study.

The addition of HD HSCT to consolidate relapse treatment did not improve the outcome of standard-risk relapse patients. This conceivably reflects the reservation of HD HSCT for patients with aggressive, refractory tumours. Our finding is consistent with that of a previously published systematic review, which summarised 19 studies and reported no EFS benefit for standard-risk relapse patient treated with HD HSCT compared with those who were not (hazard ratio: 0.97 [95% CI: 0.43–2.17] [p-value = 0.94]) [17]. Moreover, our results are in line with the current rationale for not routinely prescribing HD HSCT to standard-risk relapse patients in the UMBRELLA protocol [18].

Stage of the primary tumour and radiotherapy during relapse treatment were not associated with survival in our cohort, although previously identified as a prognostic factor for OS [4,9]. However, the vast majority of patients in our cohort had stage I primary tumours (90/109 [82.6%]), and (relapse) sample sizes were too limited to perform multivariate Cox regression analysis and rule out the potential influence of confounding factors. Moreover, information on radiotherapy as part of relapse treatment was missing for some patients and the reason for not irradiating, which may affect patient outcome, was not documented. Also in the literature, missing information or low-quality data on timing of and response to local treatment at relapse are general caveats [19].

When considering the total cohort, survival rates were comparable to the 5-year EFS of 74% and 5-year OS of 84% for standard-risk relapse patients treated with VAD (N = 12) or CyDE (N = 9) for relapse during the UKWR [8]. Fifty-eight NWTSG patients (NWTS-5) who relapsed after upfront VA therapy and who were treated for relapse with VCyED (4-year OS of 81.8% [95% CI: 66.0–90.7%] and 4-year EFS of 71.1% [95% CI: 54.2–82.8%]) had a similar outcome to our cohort as well [6]. During the preceding NWTS-2 and 3 studies, OS rates following WT relapse reached roughly 30% [20]. Included in this analysis were patients treated initially with VA or VAD (and radiotherapy) for local or metastatic primary disease of any histological type. In most cases, relapse treatment consisted of VAD. In line with our SIOP data, the improved NWTSG survival rates following relapse also suggest improved treatment intensification and stratification over time.

Finally, we were not able to identify patients who may benefit from VAD treatment instead of more intensive CyCED treatment because VAD-treated patients with excellent and with poor survival presented with identical clinical characteristics.

The UMBRELLA protocol includes well-defined risk-stratified relapse treatments and endorses next generation sequencing of primary and paired relapse WT tumour samples, providing a unique opportunity to unravel relevant prognostic factors (such as gain of chromosome 1q, which has already been associated with an increased risk of death and first recurrence [3,21,22]) and molecular targets for further patient-tailored treatment stratification at relapse [1]. In addition, early relapse prediction based on minimal residual disease, by liquid biopsy initiatives, may aid in optimising stratification [14,23].

In conclusion, in the SIOP 93–01 and the 2001 study, various salvage treatment regimens, primarily based on VAD, CyCED or ICE therapy, had been prescribed to relapsing patients initially treated with VA and without radiotherapy. Our findings suggest that a subset of patients could be adequately rescued with less intensive VAD regimens. However, to identify such patients, additional predictors for survival, for example, the molecular biomarkers under evaluation in primary tumours, could guide a more risk-tailored rescue treatment approach, which is currently based primarily on previously received therapy.

Authors' contributions

A.G. contributed to methodology, investigation, data curation, and writing the original article. H.v.T. contributed to methodology, formal analysis, investigation, and reviewing and editing the article. Y.J. contributed to formal analysis and reviewing and editing the article. R.R.d.K., G.M.V., J.G., C.R., J.P.S., C.M., K.P.-J., S.J.V., J.D., D.P. reviewed and edited the article. R.A.-S., A.C.V., G.L.R.-V., N.G., B.d.C. contributed to investigation and reviewing and editing the article. M.M.v.d.H.-E. contributed to conceptualisation, methodology, writing the original article, and supervision. J.B. and F.S. contributed to conceptualisation and reviewing and editing the article. A.M.C.M.-G. contributed to conceptualisation, methodology, writing the original article, and supervision.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.12.014.

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