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Treatment of High-Risk Relapsed Wilms Tumor With Dose-Intensive Chemotherapy, Marrow-Ablative Chemotherapy, and Autologous Hematopoietic Stem Cell Support: Experience by the Italian Association of Pediatric Hematology and Oncology

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Background. We evaluated an intensified chemotherapy strategy in children with Wilms tumor who relapsed with high-risk features. ***Procedures.*** From January 2001 to June 2006, we treated 20 consecutive children with reinduction chemotherapy (using ifosfamide/carboplatin/etoposide in 15/20 cases), with (n = 15) or without (n = 5) subsequent high-dose chemotherapy and hematopoietic stem cell support, surgery where feasible, and radiation therapy. The median time to relapse was 10 months after nephrectomy. All but two children initially received doxorubicin as first-line therapy. ***Results.*** All patients were assessed for outcome: 13 are currently alive, 12 of them in remission a median 25 months since their relapse, one with progressing tumor. The treatment was unsuccessful in eight children: the disease progressed during reinduction in three, and relapsed in five. There was one toxic death. All transplanted patients engrafted to a neutrophil count $>0.5 \times 10^3/\mu l$ after a median 11 days, and to an unsustained platelet count >25,000/μl after a median of 13 days. Three-year disease-free and overall survival rates were $56 \pm 12\%$ and $55 \pm 13\%$, respectively. Neither recurrence within 12 months of nephrectomy nor extra-lung recurrence negatively affected outcome. A survival advantage was demonstrated in patients without disease evidence prior to transplant. ***Conclusion.*** A disease-free survival rate nearing 50% is a realistic target in children with high-risk recurrent Wilms tumor. The benefit of autologous hematopoietic stem cell transplantation for consolidation deserves to be investigated in a randomized, controlled study. Pediatr Blood Cancer 2008;51:23–28. © 2008 Wiley-Liss, Inc.

Key words: autologous hematopoietic stem cell transplantation; high-dose chemotherapy; relapse; Wilms tumor

INTRODUCTION

Reported estimates of durable survival after recurrence of Wilms tumor were less than 30% in the Eighties [1–5]. Significant progress has been made the past two decades, probably due to a combination of factors, including the use of novel drugs or regimens designed with an higher dose intensity. Recent trials with high-dose chemotherapy and autologous stem cell rescue (ASCR) obtained a better outcome than in historical controls, with 3 or 4-year overall survival (OS) rates ranging from 60% to 73% [6–8]. Other investigators reached comparable results adopting intensive conventional chemotherapy, using a combination of etoposide and carboplatin with either ifosfamide or cyclophosphamide [5,9–11].

As in the case of newly diagnosed Wilms tumors, what emerges from the results with recurrent Wilms tumors is that they are clinically heterogeneous. Patients who have non-anaplastic tumors, long interval since first remission, abdominal recurrences in the absence of prior irradiation, isolated late pulmonary relapse, or who were initially given only vincristine and actinomycin-D, seem to have a relatively better prognosis at recurrence [1,5,12,13].

Based on their analysis of the European Bone Marrow Transplant Registry [14], Garaventa et al. documented that a transplant-based strategy was sporadically adopted in Italy for recurrent Wilms tumor, but with a much more flexible approach to the reinduction and conditioning regimens.

Since 2001, a standardized approach to the management of high-risk recurrent Wilms tumor has been proposed in Italy, namely dose-intensive reinduction and high-dose consolidation chemotherapy with autologous hemopoietic stem cell transplantation. The present study aims to report on the results obtained so far.

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PATIENTS AND METHODS

Patients

From January 2001 to June 2006, 19 consecutive children with Wilms tumor whose initial treatment had failed and one with recurrent clear cell sarcoma of the kidney were treated at eight

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pediatric oncology units affiliated to the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). To enter the study patients had to have at least one of the following adverse prognostic factors [1,5,6]: (1) initial stage IV; (2) tumor with anaplasia, rhabdoid tumor or clear cell sarcoma of the kidney; (2) relapse <12 months after nephrectomy; (3) doxorubicin already given; (4) second or subsequent relapse; (5) post-irradiation in-field relapse; (6) bone or brain relapse; (7) no response to first-line therapy. The original diagnosis was reviewed centrally in all cases by the AIEOP reference pathologist for renal tumors (PC). All parents gave informed consent for the participation into the trial, which was approved by the AIEOP Wilms tumor Scientific Committee, and proposed to the parents as therapeutic recommendations supported by results reportedly obtained by other groups, with consent for data collection and description.

Treatment Methods

The general study design provided for a reinduction phase based on two alternative regimens (depending on pre-exposure to ifosfamide), and a consolidation phase with high-dose chemotherapy and ASCR. The two options for reinduction chemotherapy were ifosfamide, carboplatin, and etoposide (ICE) or alternate courses of two pairs of drugs, carboplatin/etoposide, and cyclophosphamide/etoposide. ICE was administered at a lower dose (reduced-ICE) than the one used by Abu Gosh et al. [9], and consisted of ifosfamide 1,500 mg/m^2/day $\times$ 4 days, carboplatin 600 mg/m^2/day $\times$ 1 day, and etoposide 100 mg/m^2/day $\times$ 4 days. A total of four courses was recommended prior to the consolidation phase. The reinduction regimen for children who had been given ifosfamide $\leq$12 months before they relapsed consisted of alternating courses of cyclophosphamide 4,000 mg/m^2 on day 1 plus etoposide 200 mg/m^2/day $\times$ 3 days (two courses), and carboplatin 350 mg/m^2/day $\times$ 2 days plus etoposide 100 mg/m^2/day $\times$ 3 days (two courses). Since the presence of malignant cells in the bone marrow was unlikely, hematopoietic stem cells were harvested soon after the first course of chemotherapy.

All patients were evaluated for response after two courses. Surgical resection was considered after the first two courses in the event of persistent detectable tumor. Radiation therapy was evaluated case by case with the radiation therapist and was generally delivered after ASCR. Consolidation therapy consisted of melphalan 140 mg/m^2/day on day -1, etoposide 200 mg/m^2/day from day -6 to -3, carboplatin 200 mg/m^2/day from day -6 to -3 (MEC). Peripheral hematopoietic stem cells were infused on day 0. Granulocyte colony-stimulating factor was prescribed at a dose of 5 γ/kg/day from day $+4$ until neutrophil recovery.

Statistics

Event-free survival (EFS) and disease-free survival (DFS) were defined as the interval from relapse to the earliest adverse event (progressive disease, the occurrence of another relapse or death due to any cause) and to progressive disease/recurrence, respectively. OS was defined as the time from relapse to death due to any cause. Actuarial curves were constructed by the Kaplan–Meier method [15]. Subgroup comparisons were drawn using the log-rank test [16].

RESULTS

Patients

The study population consisted of 20 children treated with the intent-to-follow the guidelines above described, and they were all evaluated for outcome (Table I). The median age at diagnosis was 4.10 years (range 1.10–11.2 years). Initial treatment was according to the AIEOP Wilms tumor trials (in 13 patients) [17], and SIOP 93-01 [18] or 2001 trials (in seven patients). Apart from two patients with stages I and II tumors with a favorable histology, all the others were initially given a three-drug chemotherapy (including doxorubicin), adding carboplatin, etoposide, and ifosfamide in the three cases with unfavorable histology.

The great majority of patients had at least two risk factors (two factors in eight cases, three in eight cases, four in one case and one factor in three cases). Two children were registered at their second recurrence. The median time to relapse was 10 months after nephrectomy (range 2–138 months), with 60% of recurrences occurring within 12 months of initial nephrectomy. The lung was the only site of tumor treatment failure in 11 patients, none of whom had initially received pulmonary irradiation. The operative bed was the site of relapse in six cases (within a previously irradiated field in three cases), combined with the mediastinal lymph nodes in one case and liver in another.

Therapy

Fifteen children received reduced-ICE (for a median three courses; range 2–5); the child with clear cell sarcoma was switched to chemotherapy with topotecan because of a minor response to the first ICE course. The remaining four children had alternate combinations of cyclophosphamide, etoposide, carboplatin, and ifosfamide, including doxorubicin in two cases (Table I). In all cases, differences in the choice of drug and number of courses were based upon decisions made by the institutions concerned. The median number of CD34+ cells collected was 8.5×10^6/kg (range $5–18 \times 10^6$/kg), always through a single procedure.

Overall, 15 patients received marrow-ablative chemotherapy and ASCR. This was omitted in two patients at the discretion of institutional physician preference, and in three due to tumor progression prior to transplant. The MEC preparative regimen was adopted in eight children, while seven patients were given alternative drug combinations (Table I). Three patients were spared radiation therapy to the area of relapse: one had an isolated lung nodule that completely regressed after two ICE; one had a liver metastasis removed surgically and found completely necrotic; and one suffered from a relapse in the initially irradiated field. Four patients had up-front surgery when recurrent tumor was diagnosed. Disease status evaluation after reinduction in the 16 patients with measurable disease at baseline revealed complete response in nine cases (obtained by delayed surgery in three, and by chemotherapy in 6), partial response in four, and progressive disease in three cases. Delayed surgery consisted of the removal of a left hypochondrium mass and splenectomy, resection of liver segment VII and wedge resection of segment V, and atypical lung segmentectomy in one case each. Of the four cases achieving a partial response, three reached complete remission after the transplant, and one after radiation therapy.

TABLE I. Patient and Therapy Characteristics

Sex	Age (years)	Initial stage	Months from nephrectomy to relapse	Months from last CT	Site of relapse	Relapse in RT field?	Re-induction CT	HD-CT	Radiation therapy (Gy)	Status	DFS month	OS month
F	5	3	15	15	Pelvis	N	Other[1]	MEC	Pelvis (15)	DOT in CCR	10+	10
F	7	4	10	2	Local, mediast.	Y	ICE × 4	MEC	Abdomen, mediast. (14.4)	CCR	31+	31+
F	11.2	2 DA	33	24	Liver	N	ICE × 3	M/T	N	CCR	23+	23+
F	2.9	3	12	4	Lung	N	ICE × 4	MEC	N	CCR	14+	14+
M	4.3	3	18	11	Local	Y	ICE × 3	MEC	Flank (15, boost 7,5)	DOD, 2nd local relapse	12	27
F	3	1	5	3	Local	N	Other[2]	MEC	Flank (20)	CCR	17+	17+
M	4.8	CCSK 3	138	126	Lung	N	Other[3]	MEC	Lung (12, boost 20)	DOD, 2nd lung relapse	15	24
M	7.10	4	6	0	Lung	N	ICE × 2	MEC	Lung (12)	CCR	39+	39+
M	5	3	7	1	Lung	N	ICE × 4	MEC	Lung (12)	DOD, 2nd lung relapse	11	17
M	6.7	4	10	2	Lung	N	Other[4]	MC	Lung (10)	DOD, 2nd lung relapse	13	19
F	4.11	4	19	10	Local, liver	Y	ICE × 5	M/T	N	ED, 2nd abdominal relapse	19	21+
F	3.3	4	5	0	Lung	N	ICE × 3	None	Lung (12)	CCR	31+	31+
F	3.7	3	10	0	Lung	N	ICE × 2	HD-ICE, M/CPM	Lung (12)	CCR	15+	15+
F	1.10	4	2	0	No response	N	ICE × 3	None	Lung (12), flank (15)	CCR	19+	19+
F	3.10	2	7	1	Local	N	Other[5]	HD-ICE	Flank (19.8)	CCR	36+	36+
F	4.9	4	26	18	Lung	N	ICE × 2 + other[6]	E/T/CPM	Lung (10, boost 9.8)	CCR	79+	79+
M	4.11	4	4	0	Local	N	ICE × 4	E/T/CPM	Abdomen 21, lung (15)	CCR	46+	46+
F	4	3	6	28	Lung	N	ICE × 2	None[a]	Lung (12)	CR, initial progressive disease	3	25+
F	5.4	3 DA	3	0	Lung	N	ICE × 4	None[a]	Lung (15)	DOD, progressive disease	4	6
F	4.10	3	12	4	Kidney	N	ICE × 3	None[a]	Flank (10.8)	DOD, 2nd renal relapse	6	19

F, female; M, male; DA, diffuse anaplasia, CCSK, clear cell sarcoma of the kidney; CT, chemotherapy; N, no; Y, yes; DOT, died of toxicity; DOD, died of disese, CCR, continuous complete response, ED, evidence of disease; other: [1]cyclophosphamide (CPM)/etoposide × 2; [2]ifosfamide/doxorubicin (DOXO), ICE, CPM/DOXO; [3]ICE, topotecan/CPM × 3, CPM, topotecan/etoposide; [4]carboplatin (C)/etoposide × 4, ifosfamide/etoposide; [5]DOXO/vincristine, IFO/vincristine, CPM/etoposide; [6]CPM/DOXO/vincristine × 2; HD, high-dose; T, thiotepa; M, melphalan.
[a]Children who did not received consolidation HD-CT because of progressive disease prior to transplantation.

Survival Data

Overall, there were eight tumor treatment failures: five patients re-relapsed, and three had progressive disease while on reinduction therapy (after two, three, and four ICE courses, respectively). Only one of the three children who progressed while on reinduction was a disease-free survivor 25+ months after topotecan/vincristine and lung irradiation. Of the other two, one failed to respond to lung irradiation, and the other had a transient response to topotecan/doxorubicin/vincristine chemotherapy. After a median follow-up of 25 months (range 14–79 months), 3-year disease-free, OS and EFS were $56 \pm 12\%$, $55 \pm 13\%$, and $53 \pm 12\%$ for all patients (Fig. 1).

We analyzed the influence of baseline clinical features previously identified as prognostic, like the site of relapse, the time elapsed since initial diagnosis, the disease response after the first two courses, and the disease status at the end of induction (Table II). The 2-year DFS and OS rate for seven patients with persistent or progressive disease after the reinduction phase were 0% and $34 \pm 19\%$, respectively, as compared to $83 \pm 11\%$ and $69 \pm 15\%$ for 13 children without evidence of disease ($P = 0.003, 0.0005$) (Fig. 2). Out of 16 children evaluable for tumor response to chemotherapy, no disease-free survivors were observed among the three patients who failed to respond to the first two courses, while 3-year DFS was $58 \pm 15\%$ for 13 children who displayed objective responses ($P = 0.006$).

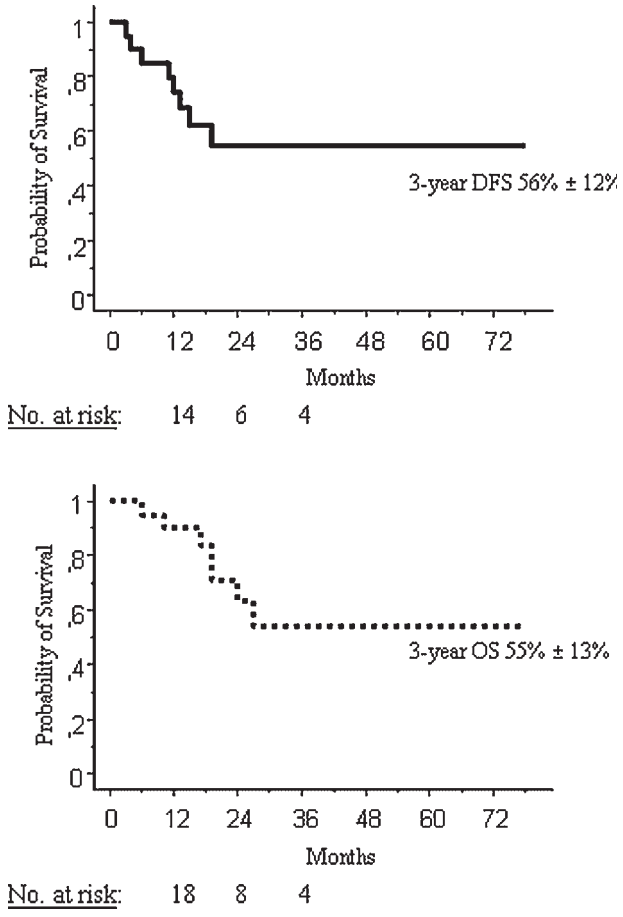

Fig. 1. Kaplan–Meier analysis of overall survival and disease-free survival for all patients.

Toxicity Data

The reduced-ICE treatment was associated with severe myelotoxicity. All patients had grade 4 hematological toxicity and multiple blood product transfusions. One patient showed signs of transient Fanconi disease. Following ASCR all children developed grade 4 neutropenia, and neutrophil recovery to $>0.5 \times 10^3/\mu l$ took a median 11 days (range 8–13 days). Platelets rose to >25,000/μl irrespective of any transfusions on day 13 (median; range 9–22). One patient showed a significant deterioration in renal function revealed after the transplant (preparative regimen with etoposide, thiotepa, and cyclophosphamide). An 8-year-old girl died in continuous remission, suffering from bacterial sepsis 4 months after transplant, after a long stay in a country outside Europe.

DISCUSSION

Recurrent Wilms tumor is infrequent, so phase II studies on novel agents are scanty and no randomized questions have been answered comparing different promising regimens. In an effort to improve outcome, chemotherapy regimens testing the efficacy of ifosfamide [19], etoposide [20], and carboplatin [21] have been used, as single agents or in combination [22]. In a review of 54 cases involved in consecutive trials at St. Jude Children's Research Hospital, Dome et al. [5] suggested that outcome has improved noticeably since around the mid-eighties, when cyclophosphamide, ifosfamide, platinum compounds and etoposide became available. The introduction of these drugs led to DFS rates for children with recurrent Wilms tumor ranging between 50% and 60% [5–7,9,11].

Features that have been associated with a worse outcome after relapse include an anaplastic histology, an interval of less than a year between nephrectomy and relapse, initial chemotherapy including doxorubicin, and relapse within a previously irradiated field [1,12]. The presence of any of these factors identifies a population recently termed as "high-risk." Not all these features are likely to carry the same weight. The NWTS-5 treated a group of relapsing children initially given only with vincristine and actinomycin D, using alternate courses of vincristine/doxorubicin/cyclophosphamide and etoposide/cyclophosphamide, and showing a 4-year EFS and OS of 71.1% and 81.8%, respectively [13]; 64% of these children relapsed within the first 11 months after nephrectomy, but this did not emerge as an adverse prognostic factor. Our analysis also revealed no evidence of an earlier relapse meaning a worse prognosis.

More recent experiences on high-risk recurrent Wilms tumor, in series ranging between 11 and 60 cases, seem to support the rationale for dose-response strategies, though there is no consensus on whether or not high-dose chemotherapy with ASCR can account for the improvement in outcome.

Abu-Gosh et al. [9] reported on 11 children treated with ICE chemotherapy, obtaining a 63.6% EFS and OS at 3 years. Malogolowkin et al. [11] recently reported for the NWTS on 60 homogeneously-treated children who relapsed after initial three-drug treatment: 4-year EFS and OS were 42.3% and 48% respectively for all patients. These results were obtained using alternate cycles of cyclophosphamide/etoposide and carboplatin/etoposide.

Other authors have investigated the role of high-dose chemotherapy and ASCR. Pein et al. [6] reported on 28 high-risk chemotherapy-responsive patients transplanted after MEC regimen, and the 3-year OS and DFS were 60% and 50%, respectively.

TABLE II. Outcome According to the Analyzed Variables

Variable	No. of patients	2-year %DFS (±SE)	P (log-rank)	2-year %OS (±SE)	*P* (log-rank)
All patients	20	56 (±12)		55 (±13)	
Relapse site					
Lung	10	48 (±16)	0.4	51 (±18)	0.6
Other	9	61 (±18)		57 (±20)	
Interval between relapse and nephrectomy					
≤12 months	13	69 (±13)	0.3	73 (±14)	0.3
>12 months	7	34 (±19)		24 (±20)	
Disease response to the first two reinduction courses					
SD, PRO	3	0	0.006	33 (±27)	0.3
PR, CR	13	58 (±15)		53 (±19)	
Disease status at the end of reinduction					
ED	7	0	0.0005	34 (±19)	0.03
NED	13	83 (±11)		69 (±15)	

SD, stable disease; PRO, progressive disease; PR, partial response; CR, complete response; ED, evidence of disease; NED, not evidence of disease.

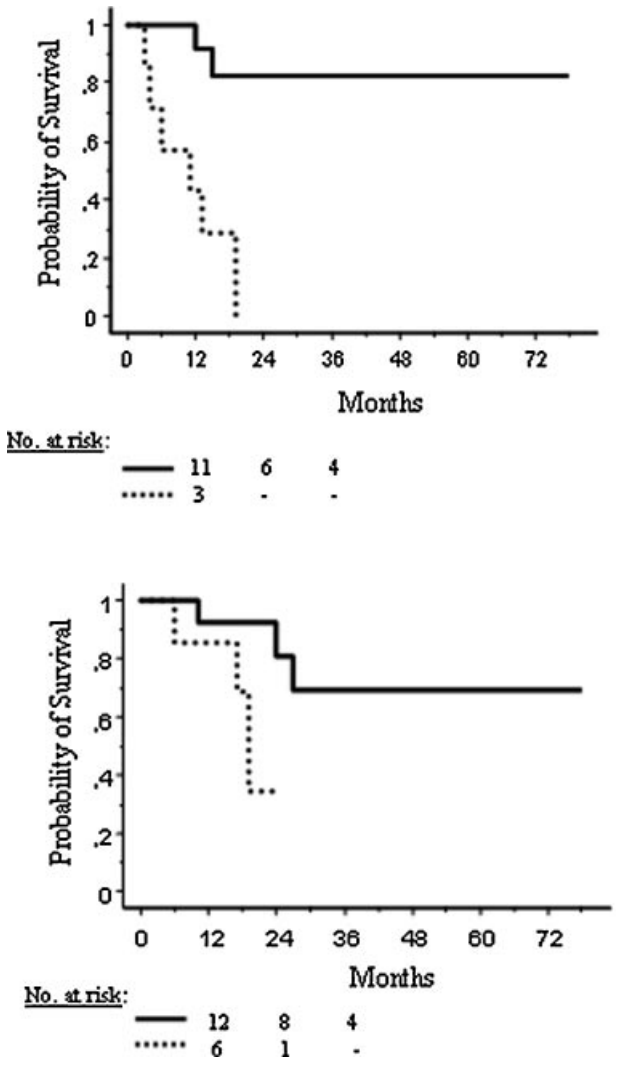

Fig. 2. Kaplan–Meier analysis of disease-free survival (top) and overall survival (below) comparing patients with (broken line) or without (continuous line) persistent or progressive disease after the reinduction.

Kremens et al. [7] described 23 cases treated with high-dose chemotherapy and ASCR (18 children had the MEC conditioning course), after various reinduction regimens: the OS was 60.9%, and the EFS 48.2%. Campbell et al. [8] showed 4-year EFS and OS rates of 60% and 73%, respectively, in 13 patients who underwent single or double ASCR after various conditioning regimens.

Italian historical data showed a 33% crude 5-year survival for 48 initially stage III–IV Wilms tumor cases treated on recurrence with conventional-dose chemotherapy (with the drug pair carboplatin/etoposide and ifosfamide/vincristine) between 1992 and 2001 (data not shown).

The primary aims of our study were to improve on the historical results and promote a uniform therapy for high-risk recurrent Wilms tumors, overcoming the tendency to adopt individualized approaches. During the same period of our study, thanks to the AIEOP Bone Marrow Transplant Registry, we found additional four eligible cases who received a marrow-ablative treatment for recurrent disease but who were not entered on our study.

One complication lies in that it was difficult to get all participating institutes to adhere strictly to our therapeutic recommendations, but this problem emerges in the literature as well [6–8]. As for the choice of preparative bone marrow ablative regimen, some patients were given the regimen with which the institution concerned was more familiar.

The 56% 3-year DFS and 55% OS are comparable with outcome in other reports on high-risk recurrent Wilms tumor, despite we electively reduced the drug dosage of the ICE and MEC associations vis-à-vis the doses used by others, in an attempt to reduce the expected toxicity. Narrowing the analysis to our 11 stage III–IV non-anaplastic Wilms tumor who received high dose chemotherapy and ASCR, in order to make a comparison with the NWTS series treated with intensive conventional chemotherapy [11], the 3-year EFS and OS were $51 \pm 15\%$ and $54 \pm 17\%$, respectively.

A potential problem in our analysis is the relative small number of patients, which is unavoidable in the setting of recurrent Wilms tumor. Factors with respect to site (multiorgan as compared with only lung) and time of relapse (interval since nephrectommy) may have shown prognostic significance had our sample size been larger. We observed that failure to achieve a complete response after the reinduction, whether with chemotherapy alone or including surgery,

identifies patients at greater risk of subsequent tumor failure. This underlines also the importance of complete surgical excision, where feasible.

In conclusion, possible future steps should include both an international cooperation to go beyond the bias of small numbers of patients treated on a national basis, and the use of less-explored agents like topoisomerase-I inhibitors [23,24]. A prospective randomized trial is warranted to investigate whether the high-dose approach with ASCR offers any advantage over conventional intensive chemotherapy, including carboplatin and etoposide with either cyclophosphamide or ifosfamide.

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