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ORIGINAL ARTICLE

SCMCIE94: an intensified pilot treatment protocol known to be associated with cure in CD 56-negative non-pelvic isolated Ewing sarcoma (EWS) is also associated with no early relapses in non-metastatic extremity EWS

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Abstract

Purpose We report the unexpected absence of early relapse (before 30 months) in 24 consecutive patients with isolated limb primary Ewing sarcoma treated with an intensified pilot protocol, SCMCIE94.

Methods Clinical data for the study were collected retrospectively from the patient files. The protocol included 6 courses of chemotherapy, split radiation, and limb salvage surgery. This SCMCIE94 protocol had been used in almost all the patients described in an earlier report, in whom those with non-pelvic isolated tumors and low/absent CD56 expression in Ewing sarcoma tumor cells were all long-term survivors.

Results The 5-year (10-year) event-free survival rate for the patients with isolated limb primary Ewing sarcoma was 78.95 ± 8.3% (68.6 ± 10.0%) and the overall survival rate was 90.7 ± 6.2% (71.1 ± 11.2%). There were no relapses before 30 months in any of these patients.

Conclusion The intensified SCMCIE94 pilot protocol has been shown previously to cure patients with localized CD56-negative non-pelvic Ewing sarcoma. The present study shows that among all patients with localized extremity disease who were treated with this protocol, there were no cases of early relapse. Although our cohort was small, the difference in results from studies using other protocols is so striking, that it would seem reasonable to assume it is attributable to the changes made in the protocol itself rather than risk factors. Late relapses of isolated limb CD56-positive Ewing sarcoma suggest minimal residual disease warranting additional therapeutic approaches such as autologous stem cell rescue after Busulfan Melfelan.

Keywords SCMCIE94 · Non-metastatic · Non-pelvic · Limb Ewing sarcoma · Treatment outcome · CD56 · Early relapse prevention

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Introduction

National and international studies conducted in the last several decades have reported improvements in the prognosis of Ewing sarcoma (EWS) using protocols with different chemotherapy agents, including actinomycin D, cyclophosphamide, vincristine [1] anthracycline (doxorubicin) [2], and most recently, ifosfamide administered together with etoposide [3]. In patients with localized disease, significant benefit has been reported for a multimodal approach consisting of multi-agent chemotherapy (neoadjuvant and adjuvant), surgery, and radiation [3]. The current 5-year overall survival (OS) rate of patients with localized EWS ranges from 65 to 75% [4]. However, analyses of different protocols reveal a widespread lack of uniformity in treatment methods, results and prognostic factors.

The SCMCIE94 pilot protocol for EWS was designed in 1993 consequent to the unsatisfactory 10-year event-free survival (EFS) results achieved with our previous protocols: 33.3 ± 7.5% for all patients, 37.5 ± 8.5% for patients with local disease, and 35.7 ± 12.8% for patients with local limb disease [5]. Owing to a lack of funding for experimental or novel therapies, we based the new protocol on available treatment elements. We hypothesized that these elements could be used more effectively without increasing toxicity based on experience from their use in other protocols in Ewing sarcoma and other diseases. The doses and total doses of specific drugs were increased to match the higher doses shown to be safe in treatment arms from other studies. Limb salvage surgery was performed, and radiotherapy was administered to all patients except for infants. This protocol is the third of the three consecutive protocols described in detail in an earlier study of 121 patients with Ewing sarcoma [5].

It was used in the study by Ash et al. [6] to treat patients with isolated non-pelvic EFS and low CD56 expression, who achieved a 100% 10-year event-free survival.

The purpose of the present study is report the unexpected absence of early relapse (before 30 months) in 24 consecutive patients with isolated limb primary Ewing sarcoma treated with this intensified SCMCIE94 protocol (Fig. 1).

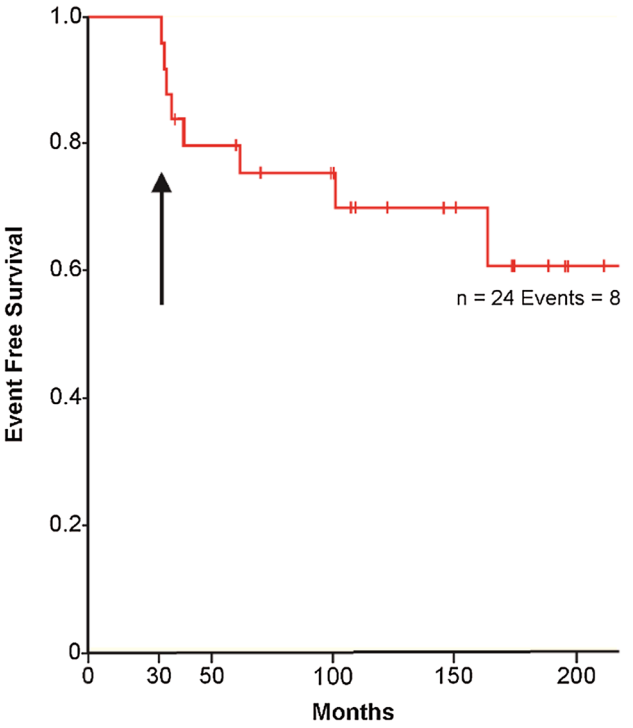

Fig. 1 EFS of patients with non-metastatic limb tumors showing the absence of early relapses before 30 months

Patient population

24 consecutive treatment-naive patients with isolated limb EWS were treated with an intensive pilot protocol SCMCIE94 from 1994 to 2011 at the Department of Pediatric Oncology of Schneider Children's Medical Center of Israel. The diagnosis was based on the light microscopy appearance of a small round-cell tumor, positive immunohistochemical studies with CD99, MIC2 antibodies, synaptophysin, chromogranin, and neuron-specific enolase, in addition to cytogenetic and molecular biology analyses for the presence of t(11:22 EWS-FLI) or t (21:22 EWS-ERG). Clinical staging was based on diagnostic imaging studies including X-rays, computed tomography, magnetic resonance imaging, and technetium 99 m bone scans. Clinical data were collected retrospectively from the patient files, including age and sex, primary tumor site, the absence of metastatic disease at diagnosis. The study was approved by the local institutional ethics committee.

Treatment protocol

The SCMCIE94 protocol (Fig. 2) contained 6 courses of a 7 drug—protocol (with doxorubicin limited to 4 courses), the timing being modified to prevent toxicity and improve efficacy.

The first two full courses (VACD-IE) consisted of 6 weekly doses of vincristine (1.5 g/m^2/week) with cyclophosphamide 700 mg/kg/day for 3 days, and actinomycin D 45 mcg/kg/day for 3 days starting with the first dose of vincristine; doxorubicin 30 mg/m^2/day for 3 days (max 360 mg/m^2) with dexrazoxane at 10–20 times the dose of doxorubicin starting with the fourth dose of vincristine;

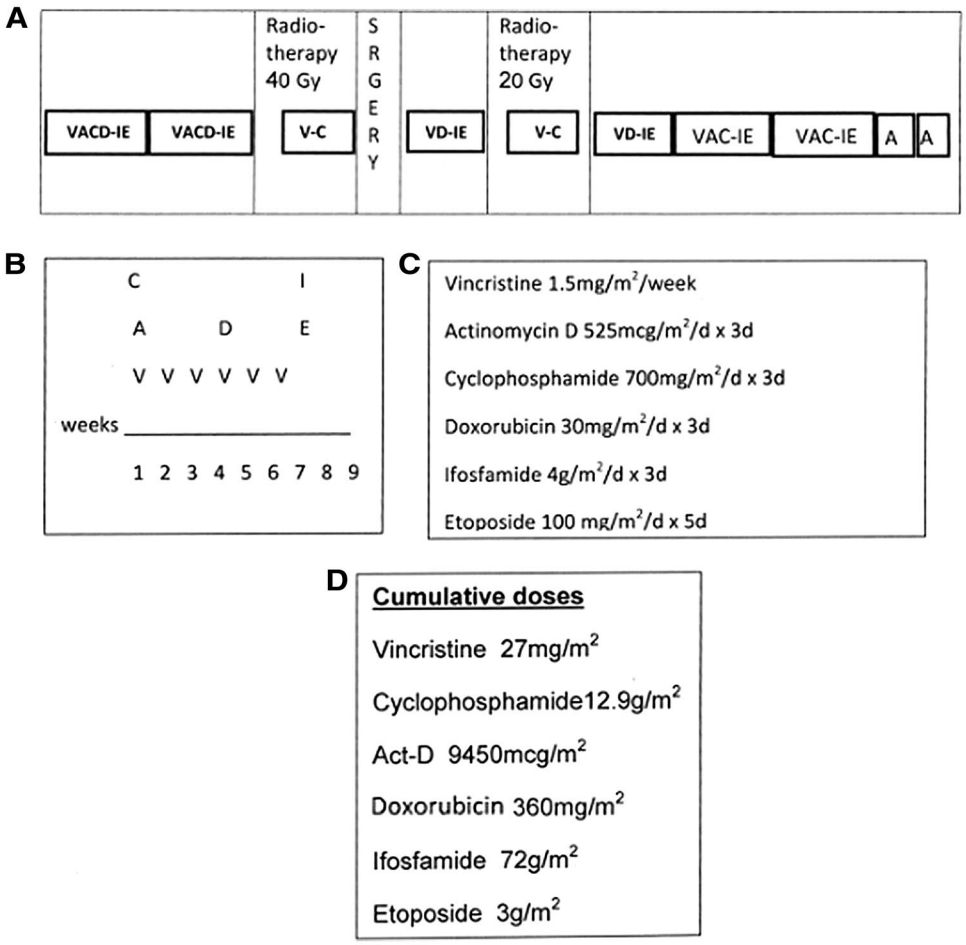

Fig. 2 Details of the SCMCIE 94 protocol for Ewing sarcoma. **A** Actinomycin was removed from cycles 3 and 4 because of the temporal proximity to radiotherapy and added at the end of therapy. Cyclophosphamide was given over 2 days at the end of radiotherapy. Doxorubicin was discontinued after cycle 4. **B** Schedule of treatment plan for the first two cycles of chemotherapy. Subsequent cycles modified as in Fig. 1a. Doses and cumulative doses of chemotherapy are shown. *V* vincristine, *A* actinomycin D, *C* cyclophosphamide, *D* doxorubicin, *I* ifosfamide, *E* etoposide. **C** Doses of chemotherapy. **D** Cumulative doses of chemotherapy in the SCMCIE94 protocol

and ifosfamide 2 g/m^2/day for 2 h every 12 h for 3 days (with the same doses of mesna) and etoposide 100 mg/kg/day for 5 days, given with the seventh dose of vincristine. Primary tumor control was obtained using radiotherapy and surgery after the second chemotherapy cycle. Radiotherapy was delivered to the tumor bed in a split dose of 40 Gy (week 18) before definitive surgery (week 26) and 20 Gy after surgery (week 36) to a total dose of 60 Gy. Cyclophosphamide 1.2 g/m^2/day together with mesna 1.2 gm/m^2 was given on the last 2 consecutive days of radiotherapy treatment. After four courses, doxorubicin was discontinued. Actinomycin D was not given after the two courses of radiotherapy but the two courses were added at the completion of therapy. The cumulative doses were as follows: vincristine 27 mg/m^2, cyclophosphamide 12.9 g/m^2, actinomycin D 9450 mcg/m^2. doxorubicin 360 mg/m^2, ifosfamide 72 g/m^2, and etoposide 3 g/m^2 (Fig. 2).

Follow-up consisted of physical examination, laboratory tests including blood count and renal function, imaging studies of the primary site and lungs, bone scans and cardiac function tests.

Statistical analysis

Data were generated using BMDP [7]. EFS and OS were estimated by Kaplan–Meier analysis. Disease recurrence or progression and secondary malignancy constituted events for EFS. Other events resulting from therapy complications and events unrelated to the disease were censored for EFS analysis. Death constituted an event for OS. Log-rank test and Wilcoxon test were used to evaluate the significance of differences in survival between groups of patients. Cox proportion hazards regression analysis was used to determine the prognostic value of clinical factors (protocol, sex, age) on survival. Statistical significance was set at $P < 0.05$.

Results

Survival rates

The 5-year EFS was 78.95 ± 8.3%, and the 10-year EFS was 68.6 ± 10.0% (Fig. 1). The corresponding values for OS were 90.7 ± 6.2% and 71.1 ± 11.2%. The median time to relapse was 35.8 months (range 30–160 months). There were no cases of relapse before 30 months from diagnosis (Fig. 1). In view of the high incidence of relapse in the first months of therapy reported by other groups (see below), the absence of early relapse in this cohort is difficult to explain by chance or by prognostic factors or reasons other than this innovative protocol of surgery, radiotherapy, and chemotherapy.

Toxicities

Secondary malignancies occurred in one patient with osteogenic sarcoma in the radiation field (3.3/12 years after first diagnosis). Limiting the dose of vincristine to a maximum of 2 mg despite the high cumulative dose seems to have prevented any long-term neurotoxicity. No cardiotoxicity was reported.

Percentage of necrosis at definitive surgery

Although the percentage of necrosis is used for assessing response after chemotherapy in Osteosarcoma [8] and also recently in Ewing sarcoma [8a], we did not find it helpful in this group of patients who had routinely received preoperative radiotherapy (see below).

Table 1 Protocol modifications adopted to intensify therapy without causing additional toxicity

Possible factors contributing to the change in relapse pattern
Radiotherapy to all patients (40 Gy pre-op, 2 Gy post-op)
Wide borders of tumor resection
Weekly vincristine
High dose CTX at end of radiotherapy
Limitation of chemotherapy-free interval
Actinomycin chemotherapy
Doxorubicin at dose of 90 mg/m^2: total dose to 360 mg/m^2
Ifosfamide 12 gm/m^2
Ifosfamide given as pulses of 2 gm/m^2 12 hourly × 6
Ifosfamide total dose 72 gm/m^2
No use of GCSF between cycles of chemotherapy
Factors limiting toxicity
Delay of Actinomycin D after radiotherapy
Dexrazoxane given with doxorubicin
Vincristine dose limited to 2 mg
Mesna given with high dose CTX as well as ifosfamide

Discussion

Protocol modifications were adopted to intensify therapy without causing additional toxicity (Table 1)

Local therapy

In the SCMCIE94, primary tumor control is achieved using radiotherapy and surgery after the second chemotherapy cycle. Radiotherapy was given to a total dose of 60 Gy. We were advised by our orthopedic partners that surgical resection is much easier if radiotherapy is limited to 40 Gy before surgery since it becomes more difficult to separate tissue planes above this dose. The remaining 20 Gy were given after surgery. The practice of irradiating all patients constitutes a very different approach to that of European groups who advocate surgery followed by radiation only for patients with large tumors or a poor pathologic response to chemotherapy, determined at the time of surgical local control. In the Children's Oncology Group (COG) protocols, postoperative radiation was used in patients with close or positive resection margins [3, 9, 10]. However, recently, the COG has presented the case for using surgery together with radiotherapy for localized Ewing sarcoma [11]. Local therapy had been shown to be important in the successful treatment of EWS. Amputation, surgery, radiotherapy to 6000 rads or partial surgery with 3000 rads was used in early studies. Radiotherapy without surgery was followed by local relapse in 21% of cases [12]. Higher local rates of local recurrence associated with metastatic recurrences and subsequent deaths have been reported in children treated within the same clinical trials who received less aggressive methods of local control [13].

The radiotherapy dose has been shown to be of importance in preventing local relapse. A study from 2004 showed that when radiotherapy was used without surgery, no local relapses occurred in patients who received 40 Gy or more to tumors measuring < 8 cm [14]. The addition of radiotherapy to increased preoperative chemotherapy may also have been of benefit in preventing the escape of residual tumor cells into the bloodstream during definitive surgery, as has been reported to occur in breast cancer [15].

We elected to use limb preservation surgery with wide margins when possible (the limb salvage resection was performed so as to be external to the tumor, and multiple samples were taken during surgery to ensure this was so).

Subsequently, this surgical concept was shown to have been appropriate. In 2000, the SSG IX study reported a 5-year OS of 90% with wide margins, 60% with marginal margins, and 0% after intra-lesional resection [16].

Protocol modification to reduce period of time without chemotherapy due to radiation and surgery

The use here of intensive chemotherapy and radiotherapy resulted in surgery being performed later than in other current protocols, i.e., at least 26 weeks from the start of therapy. This is double the time needed to complete the neoadjuvant therapy in many other studies. We were worried that the time required to administer radiotherapy and to perform surgery would result in a too-long chemotherapy-free window between the neoadjuvant and adjuvant parts of the chemotherapy. A 2009 study of osteosarcoma showed that delaying definitive surgery by more than 21 days after definitive chemotherapy was associated with an increased risk of death [17]. Therefore, to keep the interval without chemotherapy to a minimum, we administered cyclophosphamide at the end of the preoperative radiotherapy. The drug was administered over 2 days at a dose of 1.2 gm/m^2/day together with Mesna [2], before cytopenia from the radiation occurred. Surgery was performed 21 days later, and chemotherapy was restarted 21 days after surgery. The postoperative radiotherapy was delayed until after a further course of chemotherapy had been given, and again, Cyclophosphamide and Mesna were administered at the end of the radiotherapy.

Chemotherapy details

Actinomycin D has been shown to increase the radiation effect by a factor of 1.6 [18]. Therefore, we avoided concomitant radiotherapy and actinomycin treatment and administered the "missing" actinomycin at the end of the chemotherapy course.

Weekly vincristine, used in early protocols [12], has also been shown to be effective in Wilms tumor, especially with actinomycin D [19], and in low-grade gliomas together with actinomycin D or carboplatin [20]. Hemotoxicity was not a problem, and neurotoxicity, especially peripheral neuropathy, and constipation were avoided by limiting each dose to 2 mg/m^2 (maximum dosage, 2 mg) [12].

We decided to use dexrazoxane to prevent cardiotoxicity even though the suspicion that dexrazoxane was responsible for secondary malignancies had caused many centers to avoid its use in spite of the fact that there is clear evidence that the drug is cardio protective in children [21]. In retrospect, the only reports of secondary malignancies seem to be limited to Hodgkin lymphoma [22]. No cases have been reported in studies of children with acute lymphoblastic leukemia [21, 23]. Recently, dexrazoxane is being used again with doxorubicin in bone sarcomas. In a recent consensus statement, in 2017, one cooperative group recommended using dexrazoxane for doxorubicin cardioprotection in young patients with bone sarcomas [24], and in 2018, the contraindication for children and adolescents requiring high doses of anthracyclines and at risk of cardiotoxicity was removed from the European labeling for dexrazoxane [25]. At the time, this protocol was developed other groups reduced the dose of doxorubicin given or gave the doxorubicin by continuous infusion, subsequently shown not to be cardioprotective [26]. The total dose of doxorubicin in our protocol was limited to 360 mg/m^2, administered together with dexrazoxane at a dose of 10 mg/mg doxorubicin.

Ifosfamide has been shown to have a steep dose–response curve and was used here in a dose of 12 gm/m^2 given as 2 hourly pulses of 2 gm/m^2 every 12 h × 6 together with the same dose of Mesna. This has been shown to be more effective than a continuous infusion [27].

Etoposide was given together with ifosfamide because it was thought at that time to be beneficial in EWS [3].

None of the patients received granulocyte colony-stimulating factor (G-CSF; filgrastim) between cycles. This practice was based on findings that EWS cells and EWS tumors expressed both G-CSF and its receptor and that the in vivo administration of G-CSF promoted tumor growth [28].

Significance of lack of early relapse

Early relapses are the rule in reports of therapy for localized EWS. In a study of the Euro Ewing protocol, 80% of relapses occurred in the first 18 months after treatment [29]. Leavey et al. [30] reported a median time of 1.4 years to relapse (range 0–7.4) in 140 patients with local disease treated with the INT0091 protocol, and Grier et al. [3] found that 22% of patients in the arm with the best response relapsed by 2 years. In a group of patients treated from 1985 to 2002, including 55% with non-metastatic disease at diagnosis, the mean time to relapse was 17 months (range 5–90 months), and the relapse rate in the first 24 months was 71% [31]. It is relevant to note that although the recent report by Whelan et al. [32] of improved outcome when localized high risk Ewing sarcoma was treated with busulfan and melphalan (BuMel) followed by autologous stem cell rescue. Almost 30% of patients can be seen from Fig. 2 of their article to have relapsed by 30 months from diagnosis (assuming randomization was performed by 6 months of initiation of therapy). Although the inclusion criteria were very different they included patients who had more than 10% residual tumor at surgery. Patients such as these in our patient population may well have had no residual disease after preoperative radiotherapy.

Table 2 Suggestions for future protocols based on SCMCIE94

For CD56 negative non-pelvic isolated tumors
Therapy without etoposide
For all other ewing sarcomas
Discontinue etoposide
Increase dose of ifosfamide to 14 g/m^2 (7 doses of 2 g/m^2 over 2 h every 12 h) (total dose 84 g/m^2)
Increase total dose of doxorubicin 90 mg/m^2 over 3 days × 5 or 6 together with dexrazoxane (total dose 450 or 540 mg/m^2)
Give vincristine every week throughout the protocol; adjusting dose to remain same total dose
Consolidation with autologous stem cell rescue with BuMel

Series with relapse-free survival data available

In only 4 reported protocols where we able to find the data provided sufficient to calculate the period of time during which 100% relapse-free survival was maintained during treatment in patients with non-metastatic disease. The results yielded relapse-free interval of 6 months in the study of Elomaa [6], reported as local disease and metastasis-free; 15 months in the study of Marina et al. [33] based on the graphical data presented, 5 months in the study of Bacci et al. [34] in patients with local regional disease treated with the REN-3 protocol; and 7.1 months in the study of Kolb et al. [35] using the P6 protocol. However, this last report was of a much higher risk group, so the findings cannot be directly compared with our data.

Residual necrosis at definitive surgery

20 of the 24 patients in this series remain alive and well 17 with excellent necrosis (15 with100% one 99% and one 95%). One child with 30% residual tumor and an infant who had 85% necrosis without radiotherapy were both rescued with autologous stem cell rescue following conditioning with BuMel. Another infant who had 95% necrosis at operation without radiotherapy received 4500 cGy at the end of therapy and remains relapse free. The 4 patients who subsequently relapsed (after 30 moths) were 2 who had 100% necrosis one with a fracture of her involved femur before the start of therapy, and another with CD56 27%. The other two patients had major protocol violations: both received only preoperative radiation, one 50 Gy (90% necrosis) and the other 30 Gy (99% necrosis).

Previous study of patients who were treated with the SCMCIE94 protocol

Ash et al. [6], in a study of 46 patients with non-pelvic isolated EWS, described a subgroup with low CD56 cell expression (less than 26%) who had a 10-year progression-free survival rate of 100% compared to 40% in the patients with high CD56 expression. 40 of the 46 patients were treated on the SCMCIE94 protocol (five of the remaining 6 patients were treated with earlier protocols and had high CD56 expression in their tumor cells). Of the 24 patients included in the present report (without early relapse), 13 were examined for CD56 expression as part of the study by Ash et al. [6]. It follows that the patients in our cohort who had a low CD56 expression were receiving adequate therapy, and such patients could benefit from a reduction in therapy in the future (the one patient who died from a secondary osteosarcoma was not among the group evaluated for CD56 expression so we are unable to comment about the risk of secondary tumors in relationship to the CD56 status of patients).

Significance of this protocol as a basis for future protocols (Table 2)

It is not possible to determine which of the individual novel elements in this protocol accounted for the change in prognosis. We suggest that in future protocols based on these findings, therapy might be reduced in patients with isolated CD56-negative non-pelvic tumors by the discontinuation of the use of etoposide. Since doxorubicin, dexrazoxane and etoposide are all topoisomerase II inhibitors, It has been suggested that together they may increase the risk of secondary malignancy [36].

For higher risk patients (including all CD56positive tumors), etoposide should also be discontinued and other ways of increasing the efficacy of therapy should be sought.

The anticancer and cardiotoxic effects of anthracyclines seem to occur through different mechanisms. A higher cure rate in osteosarcoma has been achieved with higher doses of doxorubicin but eventually the concomitant drug-induced increase in congestive cardiac failure cancels out this increase in prognosis [37]. Dexrazoxane use makes it possible to safely increase doxorubicin to at least 450 or even 540 mg/m^2.

It has been shown possible to increase the doses of ifosfamide to 14 gm/m^2, 2 gm/m^2 × 7 every 12 h [38] (we would suggest a total dose to 84 gm/m^2). Another option is to administer vincristine on a weekly basis throughout the protocol, as a metronomic antiangiogenic element with dose

adjustment to keep the same total dosage. The recent report by Whelan et al. [32] (mentioned above) of improved outcome when localized high risk Ewing sarcoma was treated with busulfan and melphalan (BuMel) followed by autologous stem cell rescue could well be used to complement the concept presented here since their approach did not seem to prevent early relapse.

Conclusions

The intensified SCMCIE94 pilot protocol has been shown to cure patients with localized CD56-negative non-pelvic EWS. The present report further shows that none of the patients with localized extremity disease treated with this protocol had early (before 30 months) relapse. Although the patient population was small, the striking difference from the results of other protocols, in which most relapses occurred in the first months of therapy, suggests that it was the changes in the protocol that were responsible for the improved outcome. The shape of the survival curve in patients with localized high CD56 tumors indicates that minimal residual disease is the major impediment to cure in this subgroup and points to the need for additional new therapeutic approaches such as autologous stem cell rescue after BuMel.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the institutional review board of our center.

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