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REVIEW ARTICLE

Ewing Sarcoma: Current Management and Future Approaches Through Collaboration

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ABSTRACT

Ewing sarcoma (ES) is an aggressive sarcoma of bone and soft tissue occurring at any age with a peak incidence in adolescents and young adults. The treatment of ES relies on a multidisciplinary approach, coupling risk-adapted intensive neoadjuvant and adjuvant chemotherapies with surgery and/or radiotherapy for control of the primary site and possible metastatic disease. The optimization of ES multimodality therapeutic strategies has resulted from the efforts of several national and international groups in Europe and North America and from cooperation between pediatric and medical oncologists. Successive first-line trials addressed the efficacy of various cyclic combinations of drugs incorporating doxorubicin, vincristine, cyclophosphamide, ifosfamide, etoposide, and dactinomycin and identified prognostic factors now used to tailor therapies. The role of high-dose chemotherapy is still debated. Current 5-year overall survival for patients with localized disease is 65% to 75%. Patients with metastases have a 5-year overall survival < 30%, except for those with isolated pulmonary metastasis (approximately 50%). Patients with recurrence have a dismal prognosis. The many insights into the biology of the EWS-FLI1 protein in the initiation and progression of ES remain to be translated into novel therapeutic strategies. Current options and future approaches will be discussed.

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INTRODUCTION

Ewing sarcoma (ES) is an aggressive sarcoma of bone and/or soft tissue with a peak incidence during adolescence and young adulthood. In this rare disease, treatment advances since the 1970s have largely resulted from clinical trials conducted by national and international cooperative groups. Over the years, these trials have answered key chemotherapy questions and better defined risk groups, allowing tailored treatment strategies. Collaboration between pediatric and medical oncologists in ES has been a model for cancer management in adolescents and young adults. Cooperation among surgeons, pathologists, radiation oncologists, and medical and pediatric oncologists, as well as advances in diagnostic imaging, surgery, and radiotherapy technologies, has improved local disease control.

The treatment of ES relies on a multidisciplinary approach that couples risk-adapted chemotherapy and local therapy (surgery, radiation therapy, or both) to maximize the chance of cure and minimize the risk of long-term sequelae. However, although overall survival (OS) for patients with localized disease now approaches 65% to 75% (Fig 1), acute and long-term toxicities of therapy are substantial. Efforts should be pursued to better tailor therapy and especially to improve outcome for patients with metastatic and recurrent ES (Table 1).

The mutual interest of researchers and clinicians advanced the understanding of ES oncogenesis and genetic susceptibility for developing ES.[19] Since the discovery and characterization of the causal translocation involving the *EWS* gene on chromosome 22 and an ETS-type gene,[20] researchers have evaluated genes modulated by the chimeric fusion oncogene *EWS-FLI1* (and similar fusion genes) that could serve as therapeutic targets. Indeed, although targeting *EWS-FLI1* directly reverses the malignant phenotype, this finding has not been translated into clinical practice.[21]

This progress resulted from collaboration among clinicians, pathologists, and biologists at national and international levels (eg, EICESS92 [European Intergroup Cooperative Ewing's Sarcoma Study 92] and EE99 [Euro-Ewing Intergroup 99] studies) to build virtual (European Network of Excellence EuroBoNet)[22] and centralized (Children's

Study	Observed Results	Ref	Conclusions
US intergroup IESSI 1972–78 (n = 342) Localized ES	5-Year RFS VAC 24% VACD 60% VAC + Lung RT 44%	56	VAC + doxorubicin better than VAC + lung irradiation, better than VAC for metastases prevention
US intergroup IESSII 1978–82 (n = 214) Nonpelvic localized ES	5-Year RFS VAC+ Dox → High-dose intermittent CT (every 3 weeks) 73% VAC+ Dox → Moderate-dose continuous CT (every week) 56% P = .04	57	Intensive intermittent chemotherapy regimen better than moderate-dose, continuous chemotherapy
US POG CCSG INT-0091 1988–92 (n = 518) Localized and metastatic	5-Year RFS Localized / Metastatic VDC 54% / 22% VDC+ IE 69% (P = .005) / 22% (P = NS)	6	VDC + IE better than VACA for localized ES No difference for metastatic ES
US POG CCSG INT-154 1995–98 Localized ES (n = 478)	5-Year EFS VDC + IE standard (48 weeks) 70% VDC + IE intensified (30 weeks) 72% (P = NS)	21	Dose escalation of alkylating agents did not improve the prognosis of localized ES
COG AEWS0031 2001–05 Localized ES (n = 568)	5-Year EFS VDC + IE (once every 3 weeks) 65% VDC + IE (once every 2 weeks) 73% (P = .05)	61	Chemotherapy administered every 2 weeks is more effective than chemotherapy administered every 3 weeks, with no increase in toxicity
GPOH-UKCCSG EICESS92 Localized ES (n = 647)	3-Year EFS SR: Localized, < 100mL (P = NS; n = 155) → 4 VAIA → 8 VAIA 73%; 8 VACA 74% HR: Metastatic or > 100 mL → 14 VAIA 47%; 14 EVAIA 52% (P = .12)	8	Cyclophosphamide seemed to have a similar effect on EFS and OS as ifosfamide in SR patients but not enough patients to conclude with certainty In HR patients, the addition of etoposide has a nonsignificant superiority
Euro-Ewing 99 1999–2010	3-Year EFS Localized, SR: Good histologic response Or < 200 mL, RT alone (n = 856) → 6 VIDE + 1 VAI → 7 VAI 78%; 7 VAC 75% (P = NS) Localized, HR: Poor histologic response Or < 200 mL, RT alone → 6 VIDE + 1 VAI + → 7 VAI; HD Busulfan + melphalan; 7 VAI + lung RT Metastatic to lung only	15	Cyclophosphamide may be able to replace ifosfamide in consolidation treatment of standard-risk ES Ongoing comparative evaluation of long-term renal and gonadal toxicity Completed, pending results

Fig 1. Phase III randomized trials in first-line treatment of newly diagnosed Ewing sarcoma (ES) from 1970s. CCSG, Children's Cancer Study Group; COG, Children's Oncology Group; CT, chemotherapy; dox, doxorubicin; EFS, event-free survival; EICESS, European Intergroup Cooperative Ewing's Sarcoma Study; EVAIA, etoposide, vincristine, dactinomycin, ifosfamide, and doxorubicin; GPOH, Gesellschaft für Pädiatrische Onkologie und Hämatologie; HD, high dose; HR, high risk; IE, ifosfamide plus etoposide; IESS, Intergroup Ewing's Sarcoma Study; NS, not significant; OS, overall survival; POG, Pediatric Oncology Group; RFS, recurrence-free survival; RT, radiotherapy; SR, standard risk; VAC, vincristine, dactinomycin, and cyclophosphamide; VACA, vincristine, dactinomycin, cyclophosphamide, and doxorubicin; VADC, vincristine, dactinomycin, cyclophosphamide, and doxorubicin; VAI, vincristine, dactinomycin, and ifosfamide; VAIA, vincristine, dactinomycin, ifosfamide, and doxorubicin; VDC, vincristine, doxorubicin, and cyclophosphamide; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide.

Oncology Group [COG] Ewing Sarcoma Bone Tumor Bank)[23] biobanking systems. These collections contain pretreatment diagnostic ES samples (frozen, paraffin embedded) and constitutional DNA of these rare patients processed with defined standard operating procedures.

PROGNOSTIC FACTORS

Successive analyses performed by national and international collaborative studies have allowed refinement of prognostic groups and the development of risk-tailored treatment strategies. Metastatic status at diagnosis is the strongest prognostic factor across different treatment strategies, even with more sensitive imaging modalities. Five-year overall survival (OS) remains < 30% for patients with initially metastatic disease. However, those with isolated pulmonary metastasis have a better clinical outcome than those with metastases at other sites (3-year event-free survival [EFS], 29% to 52%).[3,6,13,14,17] The EE99 R3 study of primary disseminated multifocal ES identified additional prognostic factors (age at diagnosis > 14 years, primary tumor volume > 200 mL, presence and number of bone lesions, additional pulmonary metastases, and bone marrow involvement), which permitted development of a more sensitive prognostic score.[14] This score demonstrated significant differences in outcome for patients with primary metastatic disease by identifying one third of patients with a

Table 1. HDC in Ewing Sarcoma

Study	No. of Patients Treated With HDC	Metastases at Diagnosis (No. treated of overall No.)	High-Risk Localized Disease (No. treated of overall No.)	Recurrent or Progressive Disease (No. treated of overall No.)	Conclusion	Comments	Reference
Rizzoli Institute (Bologna, Italy); 1979 to 1997; retrospective study	35			35 of 195	Patients who received HDC compared with those who received conventional CT: 5-year EFS, 21% *v* 0%; Poor risk factors of second relapse: recurrence > 2 years after first treatment Importance of local treatment of primary tumor	No multivariable analysis	Bacci et al[8]
UCL (London, United Kingdom); 1992 to 2004; retrospective study	33			33 of 33	Long-term survival can be attained in patients with recurrent or refractory ES Greatest benefit observed in patients with lung-only metastases at recurrence	Various HDC regimens; potential toxicity of HDC	McTiernan et al[9]
Toronto (Ontario, Canada); 1990 to 2005; retrospective study	20	14 of 26		6 of 19	HDC may improve prognosis of children with very high–risk features (bone or bone marrow dissemination)	Small group of patients 17 received etoposide, cyclophosphamide, and melphalan; 1 received etoposide plus melphalan, and TBI; 2 received BuMel	Al-Faris et al[10]
CESS relapse registry; 2000 to 2011; retrospective study	73			73 of 239	In patients with CR or PR before HDC, multivariable regression analysis indicated absence of HDC (HR, 2.90) and early relapse (HR, 4.76) as independent risk factors	Various HDC: 15 received BuMel, 38 received treosulfan melphalan, 20 received other	Rasper et al[11]
Memorial Sloan Kettering Cancer Center; 1996 to 1998; CCG-7951; prospective study	23	23 of 32			In metastatic bone and/or bone marrow ES, no benefit of HDC	Homogenous treatment: induction chemotherapy, HDC (melphalan, etoposide, TBI) Historical comparison	Meyers et al[12]
Société Française des Cancers de l'Enfant; 1991 to 1999; prospective study	75	75 of 97			HDC may yield benefits for patients with lung-only or bone metastases	Homogenous treatment: semicontinuous cyclophosphamide, doxorubicin, IE; HDC (BuMel)	Oberlin et al[13]
					Independent prognostic factors: age, fever at diagnosis, and bone marrow involvement	Historical and literature comparison	
Euro-Ewing 99; 1999 to 2005; prospective study	169	169 of 281			Patients with bone or bone marrow metastases may survive with intensive multimodal therapy Relevant risk factors: age, tumor volume, and extent of metastatic spread	Homogenous induction chemotherapy Various HDC: 123 received BuMel, 15 received melphalan, 20 received other	Ladenstein et al[14]
Madrid (Spain); 1995 to 2009; single-institution retrospective study	47	20	27 (volume > 200 mL, inoperable tumor, or PHR)		Good outcomes, particularly in patients with: localized disease at diagnosis (78%); good performance status before transplantation; CR at time of transplantation	Heterogeneous population	Diaz et al[15]
					Among patients with metastatic disease, lung-only 56% *v* 0% other	Homogenous HDC: BuMel	

(continued on following page)

Table 1. HDC in Ewing Sarcoma (continued)

Study	No. of Patients Treated With HDC	Metastases at Diagnosis (No. treated of overall No.)	High-Risk Localized Disease (No. treated of overall No.)	Recurrent or Progressive Disease (No. treated of overall No.)	Conclusion	Comments	Reference
Italian Sarcoma Group/ Scandinavian Sarcoma Group III protocol; 1999 to 2006; prospective study	126		126 of 154 (PHR)		High-dose therapy added to VACA-IE regimen in PR patients is feasible and effective	Homogenous induction chemotherapy Homogeneous HDC: BuMel	Ferrari et al[16]
Italian Sarcoma Group/ Scandinavian Sarcoma Group IV protocol; 1999 to 2008; prospective phase II study	79	79 of 102 (lungs/pleura metastases and/or one single bone metastasis)			High-dose therapy after intensive approach and total-lung irradiation is feasible and effective Incomplete radiologic remission after primary chemotherapy is unfavorable prognostic factor	Homogenous induction Homogeneous HDC: BuMel; TBI after BuMel	Oberlin et al[16]
EBMT registry; 1980 to 2013; retrospective study	3,695	2,411 (primary multifocal and high-risk local disease)		719	Independent risk factors: age, response status, stem-cell source, BuMel HDC regimen	Heterogeneous population; various lines of treatment; various HDC regimens; only patients who received HDC; multivariable analysis	Ladenstein et al[18]

Abbreviations: BuMel, busulfan and melphalan; CCG, Children's Cancer Group; CESS, Cooperative Ewing's Sarcoma Study; CR, complete response; CT, chemotherapy; EBMT, European Society for Blood and Marrow Transplantation; EFS, event-free survival; ES, Ewing sarcoma; HDC, high-dose chemotherapy; HR, hazard ratio; IE, ifosfamide and etoposide; PHR, poor histologic response; PR, partial response; TBI, total-body irradiation; UCL, University College London; VACA, vincristine, dactinomycin, cyclophosphamide, and doxorubicin.

more favorable outcome (EFS, 40%). However, the majority still had poor (EFS, 25%) or dismal prognosis (EFS, 8%).

In localized ES, initial tumor size or volume is now commonly regarded as a strong prognostic factor, however measured and whatever the treatment. Poor prognosis is seen for large tumors defined either by a maximal diameter > 8 cm[24] or by an initial tumor volume > 200 mL.[25,26] However, for localized tumors resected after induction chemotherapy, histologic response is the strongest independent prognostic factor, overriding the impact of tumor size, regardless of the grading system[26,27] used. The Huvos-derived Salzer-Kuntschik grading system used a 10% cutoff in EE99[7] and in the previous French and German trials,[26,28-30] whereas the Italian group used a Rizzoli 3 grade system (absence of identifiable cells, presence of microscopic or macroscopic foci).[27] Initial tumor volume in unresected tumors and histologic response in resected tumors are used to tailor maintenance chemotherapy in Europe but not in North America. Other prognostic factors have been described but are not used to tailor treatment (eg, age, fever, baseline lactate dehydrogenase).[3,4,13,26,27,29-32] New tools such as early [^{18}F]fluorodeoxyglucose–positron emission tomography response will need further validation in prospective studies before their introduction into standard practice.[33,34]

Besides known clinical and histologic prognostic factors, the development of prognostic biomarkers is an exciting ongoing area of investigation, allowing the implementation of potentially more specific and less toxic therapies. Molecular characteristics and cellular behavior have been explored, but their use in clinical practice remains to be defined.[22,35-40]

Retrospective studies suggested have prognostic differences among patients expressing different *EWS-ETS* family fusion types.[35,36] However, prospective evaluation within the large EE99 trial and recent North American studies found no prognostic impact of fusion transcript type.[37,38] There is a group of Ewing-like tumors that are treated as ES even though they have fusions that join non-*ETS* genes (*NFATc2*, *SMARCA5*, *PATZ1*, and *SP3*) with (*EWSR1*) or without involvement of TET family members (*CIC-DUX4*, *BCOR-CCNB3*).[41,42] These entities likely harbor different tumor pathogenesis and might therefore have different clinical behavior or require alternative treatment strategies. There are also recurrent copy number variations of possible prognostic relevance, including gains of chromosomes 1q, 8q, and 20 and loss of chromosome 16q.[22] Whether comparative genomic hybridization profiling of the tumor might be used for classification, such as in neuroblastoma,[43] requires further study. Compelling data from retrospective studies implicate alterations of *TP53* and *CDKN2A* as negative prognostic biomarkers in ES, but their prognostic impact was not confirmed in a COG prospective study.[39] In contrast, the poor prognostic value of concurrent *STAT2* and *TP53* mutations has been reported.[40]

The prognostic value of molecularly detectable minimal disseminated disease (MRD) remains controversial.[44-46] Disseminated tumor cells in bone marrow and blood are detected at diagnosis by real-time polymerase chain reaction in approximately 20% of patients with localized ES. These patients have a clinical course similar to those with overtly metastatic ES characterized by early relapse and poor prognosis.[47] MRD detected during long-term follow-up in bone marrow and/or blood samples might identify ES recurrence in patients before its clinical manifestation.[48-50] Other ways to evaluate MRD in ES, such as flow cytometry and fluorescent in situ hybridization,[50] and next-generation sequencing–based detection of circulating tumor

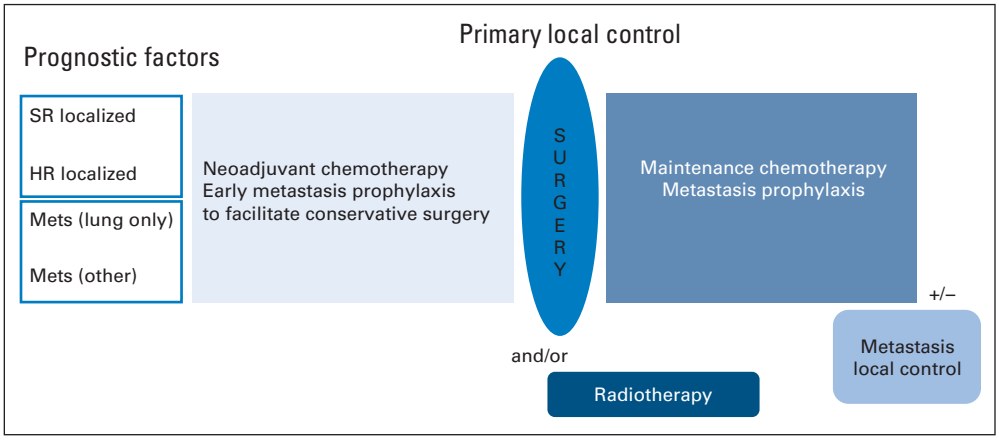

Fig 2. Current risk-adapted treatment strategy in Ewing sarcoma (ES). Strategy is adapted to metastatic status in North America, metastatic status and type of metastasis, and histologic response or initial tumor volume in localized ES in Europe. HR, high risk; Mets, metastasis; SR, standard risk.

DNA might be more easily standardized and reproduced, but their sensitivity in comparison to polymerase chain reaction remains to be defined. Prospective evaluation in large clinical trials is required to determine the most sensitive method for detecting MRD, the prognostic value of MRD, and the possible benefit of therapy modification based on MRD.

Last but not least, ES prognosis is critically determined by adequacy of local control of the primary tumor and efficacy of systemic chemotherapy to eradicate metastatic disease (Fig 2).

ES MANAGEMENT

Local Treatment: Surgery and/or Radiotherapy

The best approach for local control has evolved with time, advances in technology, and accumulating knowledge of outcomes and late effects from observational studies. A multitude of factors influence choice of local treatment (eg, patient age, site, size and local extension of tumor); however, randomized studies of local therapy approaches have been limited to two small trials evaluating radiotherapy modalities.[51,52] A future randomized local control study does not seem feasible.

The radiosensitivity of ES has been recognized since the description of this tumor by James Ewing.[53] However, radiotherapy as the single modality results in a high incidence of local recurrence (up to 30% to 35%),[54] especially for large tumors, and an increased risk of late effects (eg, growth impairment, second malignant tumors).[55,56] Surgery was gradually introduced as local treatment, and its indication was extended from expendable bones to bones requiring replacement. The development of surgical bone replacement techniques, including endoprostheses, allografts, and vascularized autografts, has helped.[55,57] However, late effects are also observed with surgery (eg, endoprosthetic infection, bone healing difficulties, fractures).[55,56] Endoprosthetic replacement in growing children is an added challenge requiring specific expertise.

Currently, tumor resection is performed whenever a marginal or wide resection seems possible, because surgical resection seems to be superior to definitive radiotherapy for local control.[4,24,31,51,54,58-60] Intralesional resection or debulking procedures followed by radiotherapy do not offer superior local control or survival compared with definitive radiotherapy and should be avoided.[59] Amputations are rarely indicated (< 10%) in patients for whom radiation therapy would likely result in poor functional results because of tumor site or age. Rotationplasty can be used in children of a suitable age as an alternative to amputation.[61]

Today, definitive radiotherapy is only advised for inoperable lesions, with a recommended dose of 54 to 55 Gy to the tumor (depending on site) with a 2-cm security margin[51] that should also include scars from surgery or biopsy. Large tumors may require higher radiation doses. However, caution is advised with radiotherapy timing and dose after busulfan-containing regimens because of the radiosensitizing effect of this agent.[17,62,63] Patients with ES have also benefitted from contemporary advances in radiation technology that spare normal tissues (eg, intensity modulated, stereotactic conditions, proton radiation therapy).[59] Fractionation does not seem to affect local control.[58] The quality of radiotherapy is essential for local control[51] and can be improved by central treatment plan review.

Debate continues about the indications for postoperative radiation therapy, because current knowledge is based on conflicting results from observational studies.[59,60,64] Postoperative radiation therapy is universally recommended in cases of incomplete surgical resection[4]; however, in Europe, patients with completely resected tumors with poor histologic response also receive postoperative radiation therapy.[26,59] Because postoperative radiation therapy is tailored to the individual patient (young age) and tumor characteristics (site, surrounding radiosensitive structures), heterogeneity is inevitable in postoperative radiation therapy decision making. Taking into account competing events, an analysis of the EE99 trial showed that postoperative radiation therapy improved local control, even after a good response to induction chemotherapy.[65] Although additional studies are required to assess the balance between postoperative radiation therapy benefits and risks, postoperative radiation therapy indications have been broadened in the Euro-Ewing 2012 trial.[66]

Preoperative radiation therapy has been introduced as a new local therapy modality in patients with expected close resection margins and when additional tumor reduction may facilitate function-preserving surgery.[59] However, interpretation of histologic response is then not reliable, because its impact on survival has not been studied after preoperative radiotherapy.

Systemic Treatment: Which Chemotherapy and Which Intensity?

Historically, the vast majority of patients treated with surgery or radiotherapy alone died as a result of metastases. In the 1970s,

cytotoxic active agents against ES included vincristine, dactinomycin, and cyclophosphamide (VAC), which were combined with doxorubicin, resulting in increased survival (IESS-I [Intergroup Ewing's Sarcoma Study I]).[1] Initially, chemotherapy was used in an adjuvant setting to control metastasis and then in a neoadjuvant setting to enhance local control (Fig 2). The importance of doxorubicin dose-intensity was demonstrated in IESS-2[2] and later highlighted in a meta-analysis.[67]

In the 1980s, the combination of ifosfamide and etoposide (IE) was found to be active in second-line ES protocols.[68] The randomized INT-0091 trial demonstrated the benefit of adding the IE combination to vincristine, doxorubicin, and cyclophosphamide (VDC) in localized ES, but there was no benefit observed in patients with metastatic disease.[3] Other investigations that replaced cyclophosphamide with ifosfamide in single-arm studies produced conflicting results.[29,52] National groups in Europe implemented randomized trials to answer these questions. The randomized EICESS-92 trial (by Gesellschaft für Pädiatrische Onkologie und Hämatologie [GPOH] and Children's Cancer and Leukaemia Group [CCLG]) addressed ifosfamide and cyclophosphamide equivalence in localized ES. Survival was similar in both arms, but the trial was only powered to show VACA versus vincristine, dactinomycin, ifosfamide, and doxorubicin (VAIA) differences of $\geq$ 15%.[6] Designed as a successor study, the large EE99 R1 trial (by GPOH, CCLG, Société Française de Lutte Contre les Cancers et les Leucémies de l'Enfant et de l'Adolescent [SFCE], and European Organisation for Research and Treatment of Cancer [EORTC]) compared cyclophosphamide with ifosfamide in combination with vincristine and dactinomycin (VAC *v* VAI) for standard-risk ES (histologic response $<$ 10% in resected tumors or initial tumor volume $<$ 200 mL for unresected tumors) in maintenance phase.[40] The conclusion of this large trial was that cyclophosphamide might be able to replace ifosfamide in consolidation treatment of standard-risk ES. The comparative evaluation of long-term renal and gonadal toxicities is ongoing and will be crucial in guiding future treatment decisions. Alternation of both agents may be a means to reduce cumulative doses of each and their late effects.

The use of granulocyte colony-stimulating factor (filgrastim) has allowed dose-intensification of chemotherapy, either by increasing the doses of cyclophosphamide and ifosfamide or by shortening the interval between treatments.[69] A COG randomized trial compared a dose-intensified chemotherapy regimen of cyclophosphamide and ifosfamide in VDC-IE with standard alkylator doses of the same regimen. No difference in outcome was observed, perhaps because of difficulties in maintaining dose-intensity of alkylating agents during treatment.[4] The next COG trial for localized ES randomly assigned patients to receive VDC-IE chemotherapy administered every 2 weeks (interval compression) versus every 3 weeks (standard). Compared with those assigned to the 3-week treatment interval, patients assigned to the 2-week treatment interval had superior 5-year EFS (73% *v* 65%; $P = .048$). There was also no increase in toxicity observed with the compressed schedule.[5]

High-dose chemotherapy followed by stem-cell rescue for ES is based on dose-response and dose-intensity relationships. Most of the single-agent high-dose chemotherapy studies used melphalan, which demonstrated transient activity in measurable tumors but did not improve long-term outcome.[70] Agents that have been used in combination high-dose chemotherapy with or without total-body irradiation include carmustine, carboplatin, cyclophosphamide, etoposide, melphalan, thiotepa, procarbazine, busulfan, and treosulfan. Several single-arm studies have explored combination high-dose chemotherapy efficacy using historical controls in poor-prognosis situations, such as recurrent or newly diagnosed metastatic tumors (Table 1). High-dose chemotherapy with busulfan and melphalan (BuMel) was initially evaluated in patients with metastatic disease. In a single-arm French study, 5-year EFS was 52% for patients with lung-only metastases and 36% for those with bone metastases.[13] At the same time, other groups achieved similar results using conventional chemotherapy and whole-lung irradiation for patients with metastatic disease limited to the lungs.[71] Resection of pulmonary metastases alone was abandoned because of lack of efficacy.[72,73] The EE99 study aimed to evaluate the best consolidation treatment after initial chemotherapy with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE)[74] by randomly assigning participants to whole-lung irradiation with conventional VAI chemotherapy versus BuMel high-dose chemotherapy without lung irradiation. Results of this trial are pending.

In the same protocol, patients with extrapulmonary metastases were treated in a single-arm study with BuMel high-dose chemotherapy after seven courses of conventional chemotherapy. OS at 3 years was 34% but varied according to the risk factors mentioned in this article.[14] In contrast, the Ewing 2008 trial is using a randomized study design to evaluate the benefit of adding one course of high-dose chemotherapy with treosulfan plus melphalan to conventional VAC chemotherapy in patients with extrapulmonary metastatic disease. The Italian (ISG) and Scandinavian Sarcoma Groups designed a joint nonrandomized study to improve the prognosis of patients with ES tumors with lung-only metastases and/or a single bone metastasis. Consolidation treatment included BuMel and whole-lung irradiation. The 5-year EFS was 43%.[17]

Other trials have questioned the value of high-dose chemotherapy. For example, a Children's Cancer Group study treated newly diagnosed patients with extrapulmonary metastases with VDC-IE chemotherapy followed by high-dose chemotherapy with melphalan and etoposide plus total-body irradiation. The 23% 2-year EFS was identical to that achieved with conventional chemotherapy alone.[12] On the basis of the 30-year experience with high-dose chemotherapy, the European Society for Blood and Bone Marrow Transplantation concluded that this approach improved results in high-risk patients and favored busulfan-containing high-dose chemotherapy.[18] Two cooperative groups used BuMel as consolidation treatment for high-risk localized ES defined by poor histologic response to induction chemotherapy,[16,30] with improved survival as compared with historical controls and survival similar to that of standard-risk patients.[58] These studies, which showed a potential benefit of this strategy, were the basis of EE99, the results of which are still pending.

The COG investigated the feasibility of a metronomic treatment using vinblastine plus celecoxib combined with VDC-IE (AEWS02P1 [American Ewing Sarcoma Study 02P]) in metastatic ES. Although feasible according to protocol definitions, excess toxicity in irradiated tissues was noted and has limited the use of this regimen. In addition, the 24-month EFS was only 35% (71% for lung-only *v* 26% for extrapulmonary metastases).[75]

Current Phase III Studies

There are several randomized trials ongoing for localized ES (Fig 3), with age inclusion criteria chosen according to disease epidemiology (age $<$ 35 to 50 years). VIDE induction chemotherapy is now considered the standard chemotherapy for ES in Europe, whereas

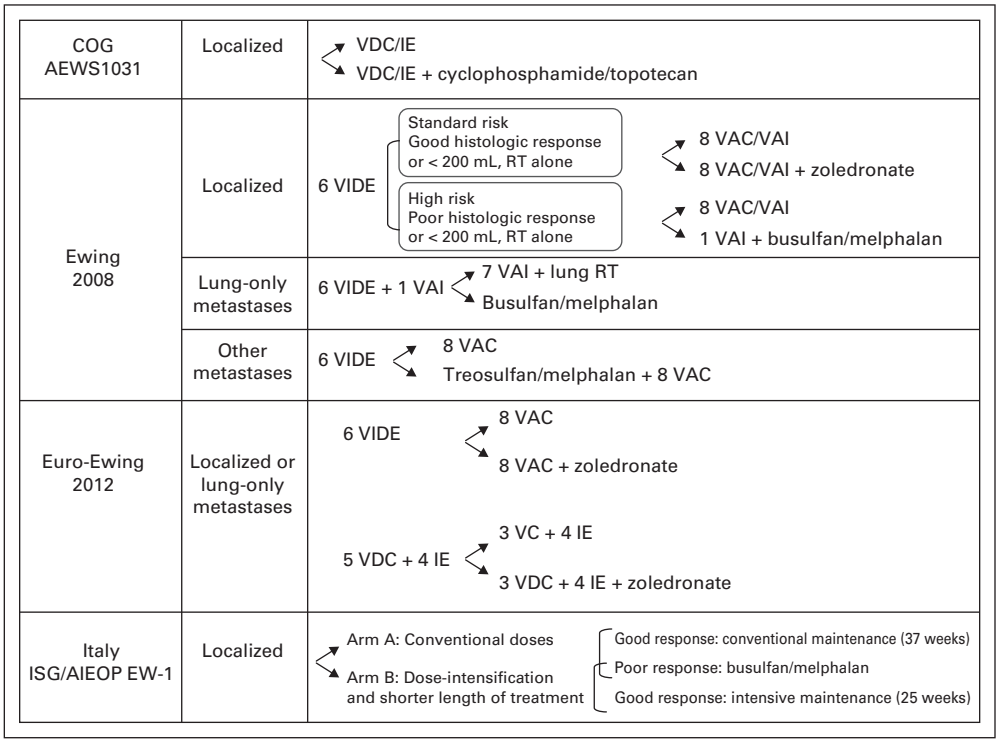

Fig 3. Randomized trials ongoing for localized Ewing sarcoma. AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; COG, Children's Oncology Group; IE, ifosfamide plus etoposide; ISG, Italian Sarcoma Group; RT, radiotherapy; VAC, vincristine, dactinomycin, and cyclophosphamide; VAI, vincristine, dactinomycin, and ifosfamide; VC, vincristine plus cyclophosphamide; VDC, vincristine, doxorubicin, and cyclophosphamide; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide.

compressed VDC-IE is the North American standard. The results of the ongoing Euro-Ewing 2012 trial comparing these regimens will define the international standard induction chemotherapy for ES. The possible benefit of zoledronic acid added to conventional maintenance chemotherapy is currently being evaluated in both Euro-Ewing 2012 and Ewing 2008 trials, and a prospective meta-analysis is planned. On the basis of the efficacy of the cyclophosphamide plus topotecan combination observed in recurrent ES, the COG-AEWS1031 trial is currently evaluating the addition of this combination to compressed VDC-IE. Finally, the ISG and Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) are conducting a randomized trial for patients with nonmetastatic ES, comparing a prolonged versus shorter dose-intensive treatment.

REFRACTORY AND RECURRENT DISEASE

The prognosis of refractory or recurrent ES remains dismal. Even after limited localized relapse, the long-term survival is 22% to 24% and is even lower for patients with distant relapse.[76] To date, no standard treatment has been defined in such a setting. Several combinations of agents have shown promising responses in retrospective or phase II studies, such as topotecan plus cyclophosphamide,[77] temozolomide plus irinotecan,[78] gemcitabine plus docetaxel,[79] and high-dose ifosfamide.[80] The first Euro-Ewing Consortium (EEC) study for recurrent ES (REECUR) will feature a randomized phase II/III trial with multi-arm multi-stage design comparing these four regimens to identify the optimum one based on the balance between efficacy and toxicity. However, initial response to chemotherapy does not translate into prolonged survival, especially for early recurrences,[81,82] underscoring the need for novel consolidation strategies. Randomized controlled trials are needed to establish the role of high-dose chemotherapy in tumors that respond to second-line therapy, because conflicting results have been reported in retrospective and single-arm studies.[83] There is also an urgent need for new strategies combining targeted therapies with chemotherapy regimens of established efficacy, because targeted therapies alone are unlikely to cure patients with ES recurrence.

NEW TARGETS

Despite the EWS-FLI1 fusion protein driving ES oncogenesis, it has proven to be a poor target for drug development (transcription factor of nuclear localization). Presently, the most promising targeted therapies are those acting on the microenvironment (Fig 4).

Several drugs have been identified using *EWS-FLI1* signature-based approaches that mimic the effects of EWS-FLI1 knockdown. Agents directly targeting the EWS-FLI1 interaction with partner proteins (RNA helicase A) in the transcriptional complexes are in the preclinical optimization phase (eg, small-molecule YK-4-279 and peptide ESAP1).[84] Other identified agents are chemotherapy drugs with established clinical efficacy (eg, doxorubicin and etoposide) and agents under evaluation, such as the broad-spectrum protein kinase inhibitor midostaurin[85] (phase I trial in leukemia; ClinicalTrials.gov identifier NCT01174888) and the antineoplasic antibiotic-inhibiting RNA synthesis mithramycin[86] (ongoing phase I trial in EW; ClinicalTrials.gov identifier NCT01610570). However, this approach has been criticized, because cytarabine identified by a similar preclinical screen failed to show efficacy in an ES phase II trial.[87] *EWS-FLI1*–specific expression signatures have also been the basis for integrated genomic approaches to identify key downstream pathways for potential therapeutic drugs inhibiting the deregulated EWS-FLI1 effectors.

The insulin-like growth factor-1 receptor (IGF1R) –targeting strategy, an initially promising therapy based on evidence of IGF1

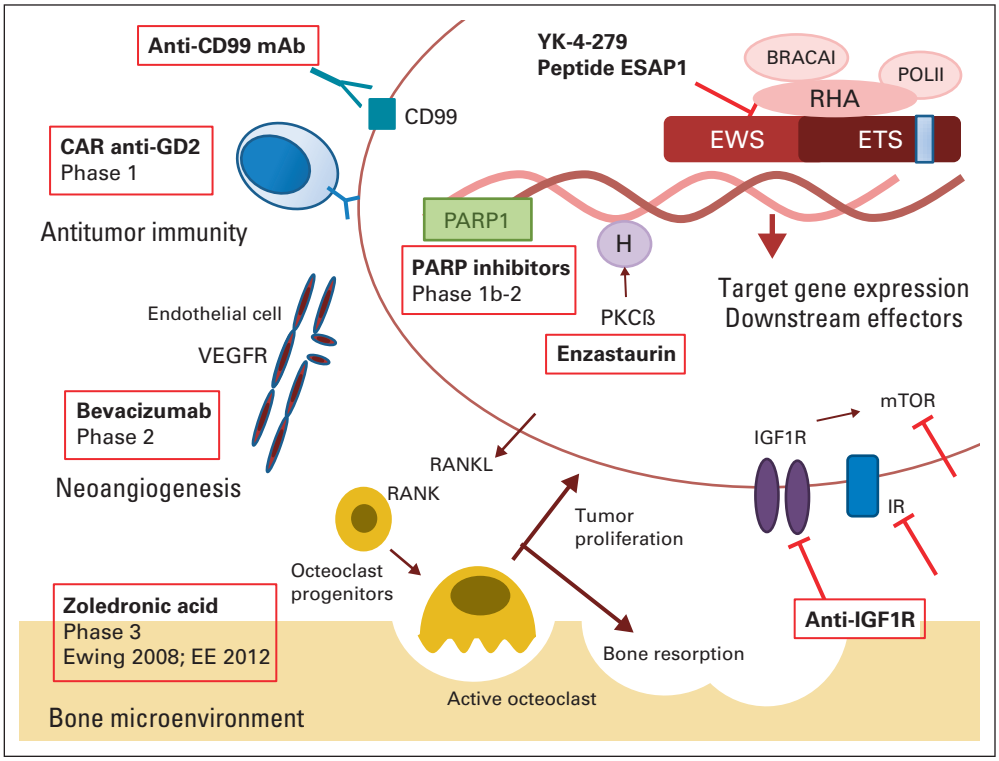

Fig 4. Some new potential targets in Ewing sarcoma. CAR, chimeric receptor gene-modified T cell; EE 2012, Euro-Ewing 2012; H, histone; IGF1R, insulin-like growth factor receptor-1; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase; PKC, protein kinase C; RANKL, RANK ligand; RHA, RNA helicase; VEGFR, vascular endothelial growth factor receptor.

signaling in ES, has not resulted in significant new therapeutic approaches. The clinical application of IGF1R-directed antibodies or small-molecule inhibitors produced dramatic but transient responses in a few patients (10%) with refractory disease, albeit prolonged disease control in a tiny minority of patients. Because of modest success against a variety of cancers in single-agent studies, pharmaceutical companies dropped these agents, although a randomized trial with and without an IGFR1 antibody, in combination with VDC-IE chemotherapy, for metastatic ES is planned by COG. Alternatively, up-regulation of IGF1R or mammalian target of rapamycin suggests a potential mechanism of resistance, calling for cotargeted approaches.[88] However, the pathophysiology of the dramatic response to IGF1R inhibition and predictive biomarkers in the small population of responders remains unknown.

Poly (ADP-ribose) polymerase 1 (PARP1) is a key enzyme involved in single-strand repair of DNA and a cofactor for *EWS-FLI1* DNA binding.[89] In vitro and in vivo ES models are highly sensitive to the PARP1 inhibitor olaparib alone and in combination with temozolomide.[89] Drug screening of several hundred cancer cell lines identified marked and selective susceptibility of ES cell lines to olaparib.[90] PARP1 inhibitors alone or in combination with temozolomide have already entered ES clinical trials enrolling adults and children. DNA repair potential biomarkers currently exist (eg, *H2AX*, poly [ADP-ribose]).[91] Assays are under development to analyze PARP1 inhibitor activity in peripheral-blood cells as a potential surrogate for tumor biopsies.

EWS-FLI1 directly regulates epigenetic mechanisms of gene repression, which involves the direct EWS-FLI1 target gene *PRKCβ*.[92] *PRKCβ* loss induced apoptosis in vitro and prevented tumor growth in vivo in ES models. Enzastaurin, a protein kinase C inhibitor, has been tested in lymphoma and carcinoma but not as yet in sarcoma.

Some tumor microenvironment–targeted therapies developed for other tumor types are currently being tested on ES. Bevacizumab is an anti–vascular endothelial growth factor (VEGF) immunoglobulin G1 monoclonal antibody which inhibits VEGF/VEGF receptor-1 and VEGFR receptor-2 interactions and VEGF-dependent angiogenesis. A randomized phase II trial of bevacizumab combined with vincristine, topotecan, and cyclophosphamide in first recurrent ES showed good tolerance (COG AEWS0521; ClinicalTrials.gov identifier NCT00516295). Antiangiogenic multikinase small-molecule inhibitors are also being tested (eg, regorafenib; ClinicalTrials.gov identifier NCT02048371).

Bone tumors are characterized by a combination of tumor growth and osteolysis, marked by the activity of RANK and its ligand (RANKL).[93] RANKL facilitates osteoclastogenesis, bone resorption, and growth factor secretion, leading to bone destruction, tumor growth, and intraosseous migration of RANK-positive cells.[93] Zoledronic acid, a potent inhibitor of bone resorption, inhibits RANK expression and osteoclast progenitor migration during osteoclastogenesis and increases osteoprotegerin expression. In in vivo ES models, zoledronic acid is only active against the bone tumor. An effect on extraosseous tumor components is obtained when zoledronic acid is combined with ifosfamide.[94] Two randomized trials are evaluating the added benefit of zoledronic acid in combination with first-line chemotherapy for localized ES maintenance treatment (Ewing 2008 and Euro-Ewing 2012).

The ganglioside GD2 is a neuroectodermic marker expressed in human ES. Chimeric antigen receptor gene-modified T cells from healthy donors and a patient exerted potent GD2-specific cytolytic responses to allogeneic and autologous ES, including tumor cells grown as multicellular anchorage-independent spheres. GD2-specific

T cells further had activity against ES xenografts.[95] A phase I study to determine the feasibility of producing anti-GD2 chimeric antigen receptor cells and the safety in children and adults with GD2-expressing solid tumors other than neuroblastoma is ongoing (ClinicalTrials.gov identifier NCT02107963). Another interesting immune strategy in ES is anti-CD99 monoclonal antibodies, which showed additive growth inhibitory effect with doxorubicin in preclinical ES in vivo models.[96]

DISCUSSION

The optimization of ES multimodality therapeutic strategies has resulted from the efforts of national and international groups in Europe and North America and from cooperation among multidisciplinary investigators. Successive first-line trials have addressed the efficacy of various cyclic combinations of drugs and identified prognostic factors used to tailor therapies, although the place of high-dose chemotherapy is still debated. However, outcomes for patients with metastatic and recurrent ES remain poor, because most are incurable with current chemotherapy regimens and strategies. A better understanding of ES biology is critical to understand oncogenesis and metastatic processes, unveil mechanisms of resistance, and identify novel therapies. With increasing knowledge, prioritization of marker, target, and drug selection for ES clinical trials will be the next international collaborative challenge. The first European Network for Cancer Research in Children and Adolescents (ENCCA)–supported European Interdisciplinary ES Research Summit held in Vienna, Austria, in 2011 assembled 30 European and five North American expert scientists to address this goal.[22]

The development of biomarkers predictive of therapeutic response is crucial and must accompany drug development from the start. Because successive biopsies might be problematic, biomarker assessment in peripheral blood is appealing, especially in children. Successful validation of predictive biomarkers in concert with clinical assessment of drug efficacy will ensure that the potential benefits of these agents are investigated as expeditiously as possible. Traditional therapeutic approaches including dose-dense chemotherapy and multidisciplinary approaches have led to impressive cure rates of approximately 65% to 70% for patients with localized disease. However, new therapeutic approaches, such as targeted therapy, are required to improve outcomes for patients with metastatic tumors and relapsing or refractory disease and potentially may further improve outcomes for patients with localized disease with reduced toxicity profiles.

Elucidation of ES biology offers promise for identifying novel potential therapeutic targets. The challenge for the future will be their integration into phase III protocols while demonstrating their benefit in improving patient outcomes. Such integration will necessitate new study designs to minimize the required number of patients and the length of study accrual. Selection of patients, matching patient-specific oncogenic pathways with the mode of action of specific drugs, could be (among others) one of the new trial designs. Increased collaboration among clinical cooperative groups and among industry and cooperative groups is essential to further improve ES prognosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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