

Management of Ewing sarcoma family of tumors: Current scenario and unmet need

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Abstract

Ewing sarcoma family tumors (ESFT) are heterogeneous, aggressive group of disease with peak in-

cidence in adolescent and young adults. The outcome has been improved dramatically from 10% with surgery and radiotherapy alone to 65%-70% now, in localized disease, with the introduction of chemotherapy. Chemotherapy regimen evolved from single agent to multiagent with effort of many cooperative clinical trials over decades. The usual treatment protocol include introduction of multi-agent chemotherapy in neoadjuvant setting to eradicate systemic disease with timely incorporation of surgery and/or radiotherapy as local treatment modality and further adjuvant chemotherapy to prevent recurrence. Risk adapted chemotherapy in neoadjuvant and adjuvant setting along with radiotherapy has been used in many international collaborative trials and has resulted in improved outcome, more so in patients with localized disease. The role of high dose chemotherapy with stem cell rescue is still debatable. The outcome of patients with metastatic disease is dismal with long term outcome ranges from 20%-40% depending on the sites of metastasis and intensity of treatment. There is a huge unmet need to improve outcome further, more so in metastatic setting. Novel therapy targeting the molecular pathways and pathogenesis of ESFT is very much required. Here we have discussed the current standard of management in patients with ESFT, investigational targeted or novel therapies along with future promises.

Key words: Outcome; Review; Chemotherapy; Ewing sarcoma; Targeted therapy; Radiotherapy; Prognostic factors

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Core tip: Ewing sarcoma family tumors are a heterogeneous and aggressive group of disease of bone and soft tissue in childhood. The outcome has improved with introduction of chemotherapy and multimodality management. But, the prognosis of patients with metastatic disease is dismal. Novel targeted therapies

are investigational and may offer some hope in future, especially in metastatic setting. In this review we have discussed current treatment modality, prognostic factors, ongoing trials and novel investigational therapies.

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INTRODUCTION

Ewing sarcoma families of tumors (ESFT) are a heterogeneous and aggressive group of disease of bone and soft tissue that includes classical Ewing sarcoma, peripheral primitive neuroectodermal tumor and Askin tumor. It is the 2nd most common primary malignant bone tumor (34%) after osteosarcoma^[1] with peak in 2nd decade of life, though approximately 20% to 30% of all cases occur in 1st decade. Over the last four decades, the survival has been improved from 10% with radiotherapy alone to near 70%, in localized disease, with the introduction of chemotherapy and multimodality approach. This improvement in outcome has been achieved after many international collaborative clinical trials and close liaison between orthopedic surgeons, adult and pediatric oncologists, radiation oncologist, pediatric surgeons, biomedical engineers, pathologists and radiologists as well as invention of better diagnostic imaging, radiotherapy techniques and prosthesis.

With the improvement in outcome and more number of long-term survivors, the focus is now on to minimize toxicities, such as chemotherapy related, radiotherapy related and surgery related long-term complication without compromising the oncological outcomes. The multidisciplinary approach with risk adapted chemotherapy and local treatment (surgery and/or radiotherapy) has been used in recent times in many collaborative trials to minimize the overtreatment and thus treatment related side effects with maintaining high cure rates. This approach is the current standard of care in maximum institutions all over the globe.

Even with current armamentarium the outcome of ESFT patients with metastatic disease is dismal with cure rate varying between 20%-40%^[2,3] and even less in those with recurrent/refractory diseases. The current emphasis is to improve the survival outcome in ESFT patients with metastatic disease and also in the recurrent setting. There is a vacuum in novel and targeted therapies as compared to adult solid tumors, and there lies a huge unmet need to improve the outcome of poor risk ESFTs.

Researchers across the world have tried to understand the pathogenesis of ESFT along with the molecular downstream pathways enhancing the survival of ESFT tumor cells. The primary focus was on *EWS-FLI1* fusion

oncogene, and other similar fusions that were thought to drive the oncogenic pathway in ESFT, but targeted therapy by blocking its product has not resulted into any meaningful clinical outcome^[4,5]. In this review we have discussed the current standard of treatment-chemotherapy, local treatment modalities, role of high dose chemotherapy, and salvage treatment along with novel targeted therapies under investigation and potential future promises.

WHAT ARE THE CLINICALLY RELEVANT PROGNOSTIC FACTORS?

Many international cooperative trials has been performed over last four decades to improve the outcome of ESFTs and further analysis of those studies revealed many prognostic factors that predicted differential outcomes and successively helped in designing tailored clinical trials to optimize the treatment strategies depending on the risk group and to decrease over treatment and treatment related side effects. Further refinements and validation of those prognostic factors (clinic-pathological and treatment related factors) has been done in further studies and in routine clinical practices. Amongst all the clinic-pathological and treatment related factors, presence of metastasis at baseline is the strongest prognostic factor and has been proven in all clinical studies and routine clinical practices. The prognosis also depends on burden of metastasis and site of metastasis. Spectrum of outcome varies from worst with bone marrow metastasis (3-year EFS of < 10%) with non-pulmonary metastasis in the middle and single pulmonary metastasis having the best outcome (3-year EFS of 40%-50%)^[6-10]. No research group or study had prospectively evaluated the prognostic significance of burden of metastasis until recently. Study from our center in ESFT patients with metastatic disease found hypoalbuminemia (< 3.5 g/dL) as a novel and independent poor prognostic factor to affect outcome^[2]. The recent EuroEwing 99 (EE99) systematically risk stratified the metastatic group and the 3rd randomized arm (disseminated multifocal ESFT) identified novel prognostic factors, such as - age at diagnosis > 14 years, presence and number of bone metastasis, number of pulmonary metastasis and bone marrow involvement and also developed a prognostic score to predict differential outcome ranging from 8%-40%^[10].

Systemic symptom (fever and weight loss) is a poor prognostic factor along with high lactate dehydrogenase level that denotes tumor burden. These two prognostic factors has been used to risk stratify ESFT patients to tailor therapy. Tumor size and tumor volume is well established prognostic across the clinical studies with tumor size > 8 cm^[11] and tumor volume > 200 mL^[12,13] is poor prognostic and has been used in all clinical trials for risk adapted therapies. Site of primary tumor is also of prognostic significance with axial primary especially pelvic location is poor prognostic. Both tumor size and pelvic primary has been proven as poor prognostic in

our institutional experience^[2,14]. But recently histological response to neoadjuvant chemotherapy (poor response has been defined as > 10% viable tumor cells as per Salzer-Kuntschik grading system^[13]) has been emerged as the strongest prognostic factor overriding tumor size, tumor volume or tumor location. The recent EE99 study risk stratified ESFT patients in respect to histological response to chemotherapy to tailor therapy^[15]. WBC count has been emerged as independent prognostic factor in our experience of ESFT^[14,16-18] treated with uniform chemotherapy protocol with high WBC (> 11000/ μ L) having poor outcome. It may signify micrometastatic disease and inflammatory nature of the disease and will require further validation in a prospective study.

Collaborative efforts have been made to identify potential biomarker in this rare aggressive tumor. Early retrospective studies^[19,20] reported prognostic significance of different transcripts (*EWS-ETS* fusion types) but failed to do so in prospective studies^[21]. High throughput methods has revealed gene copy number variations^[22], such as - 1q-, 18q-, 20-, 16q+ along with mutation in *TP53*, *CDKN2A* and *STAT2* and concurrent presence of *STAT2* and *TP53* reported as poor prognostic^[23]. Detection of disseminated tumor cells in blood and bone marrow^[24] in localized patients (up to 20%) found to poor prognostic and its detection after completion of therapy (minimal residual disease) by flow cytometry or other sensitive method can tailor therapy, detect early recurrence and can be of future prognostic significance^[20].

WHAT IS THE ROLE OF BIO-IMAGING?

Histological response to neoadjuvant chemotherapy is the strongest prognostic factor in localized ESFT and metastatic disease is the strongest one in whole cohort of ESFT. Efforts have been made to predict metastatic potential of ESFT in view of its aggressive nature and to escalate therapy in case of poor responder before initiation of local therapy. 18F-FDG PET is a relatively non-invasive test that can escape invasive diagnostic metastatic work-up like bone marrow aspiration/biopsy and tissue diagnosis in case of doubtful lung metastasis if it predicts site of metastases, and also post chemotherapy response assessment before the histological response is assessed. Retrospective studies have shown it can predict response to neoadjuvant chemotherapy and have a high concordance rate with the histological response by measuring reduction in standardized uptake value^[25,26] and also reduction in metabolic tumor volume^[27]. But no prospective study has been done in regards to its predicting power of detecting metastasis and to predict response to chemotherapy before its utilization in routine clinical practice.

LOCALIZED DISEASE

What chemotherapy, what intensity, and how long?

Historically, in early 1970s the outcome of ESFT with

radiotherapy and surgery alone was dismal with only < 10% patients surviving and all invariably experienced relapse within 2 years. With the introduction of chemotherapy the outcome have improved drastically to 70% cure rate in localized disease. The evolution of chemotherapy started from single agent vincristine to multiagent chemotherapy (VAC - vincristine, actinomycin D and cyclophosphamide) and from adjuvant to neoadjuvant setting (Table 1). Then comes the role of anthracyclines and addition of doxorubicin resulted in improved survival in 342 localized ESFT along with additional benefit of whole lung irradiation (WLI) in metastasis prevention in Intergroup Ewing's Sarcoma Study 1 (IESS-1)^[28]. The value of doxorubicin further potentiated in IESS- II which showed that high dose intermittent doxorubicin is better than low dose continuous therapy in 214 non-pelvic localized ESFT^[29]. The landmark United States intergroup study (INT0091) by Grier *et al*^[6] showed additional benefit of ifosfamide and etoposide (IE) in addition to vincristine, doxorubicin, cyclophosphamide (VDC) in localized patients with ESFT after the beneficial effect of IE has been demonstrated in recurrent setting^[30], but the trial failed to demonstrate any benefit of IE in a relatively smaller numbers of patients with metastatic disease. Replacement of ifosfamide with cyclophosphamide has showed conflicting results^[31] and EICESS-92 trial showed similar result with four drug chemotherapy regimen in a relatively underpowered study of 155 localized ESFT along with non-significant advantage of addition of etoposide in metastatic disease^[7]. In a different strategy to improve outcome by intensifying the alkylator dose and thus reducing the chemotherapy duration to 30 wk as compared to standard 48 wk with VDC-IE failed to improve outcomes in a United States intergroup trial (INT 154)^[32]. But subsequent Children Oncology Group (COG) study used dose compressed study of 3-weekly vs 2-weekly VDC-IE with use of filgrastim, thus maintaining the dose intensity, and demonstrated superior outcome in 2-weekly arm (5-year EFS of 73% vs 65%, $P = 0.048$)^[33] without any increasing toxicity in the experimental arm. The latest and largest trial in ESFT is the ongoing EE99 trial that compared cyclophosphamide with ifosfamide in standard risk ESFT and the early result showed equivalent outcome in both arm with pending long-term toxicity results^[15] (Table 2). The role of high dose chemotherapy with autologous stem cell rescue not well studied in localized disease as consolidation in comparison to continuation or maintenance chemotherapy. Two cooperative trials^[34,35] used BuMel conditioning regimen with stem cell rescue as consolidation therapy in a non-randomized manner in high risk localized disease (defined as poor histologic response to chemotherapy) and showed improved survival as compared to historical control and similar to that of standard risk patients. Following that result the recent ongoing EE99 trial randomized (arm 2) BuMel based high dose chemotherapy vs continuation of standard chemotherapy after VIDE induction chemotherapy in high risk localized patients and the result is still pending (Table 2).

Table 1 Randomized studies of chemotherapy in upfront treatment of Ewing sarcoma family tumors

Study	Patients (n)	Intervention ¹	Outcome	P	Comments
IESS I ^[78]	Localized (342)	(1) VAC (2) VACD (3) VAC + Lung RT	5-yr RFS 24% 60% 44%	–	Beneficial of doxorubicin and benefit of lung RT
IESS II ^[29]	Non-pelvic, localized (214)	VACD (1) Intermittent, high dose (3 weekly) (2) Continuous, moderate dose (weekly)	5-yr RFS 73% 56%	0.04	Intermittent, high dose better
POG-CCSG INT-0091 ^[6]	Localized (398)	(1) VDC (2) VDC + IE	5-yr RFS 54% 69%	0.005	IE is beneficial in addition to VDC in localized but not in metastatic disease
	Metastatic (120)	(1) VDC (2) VDC + IE	22% 22%	NS	
POG-CCSG INT-154 ^[32]	Localized (478)	(1) VDC + IE (standard) (2) VDC + IE (intensified)	5-yr EFS 70% 72%	NS	Dose intensification not effective
COG AEWS0031 ^[33]	Localized (568)	(1) VDC + IE (3 weekly) (2) VDC + IE (2 weekly)	5-yr EFS 65% 73%	0.05	3-weekly better than 2-weekly with no increase in toxicity
EICESS92 ^[7]	n = 155	SR (localized and < 100 mL)	3-yr EFS	NS	Cyclophosphamide and ifosfamide is similar in efficacy in SR patients
	n = 492	4#VAIA → 8#VAIA vs 8#VACD HR (metastatic, > 100 mL) 14#VAIA vs 14#EVAIA	73% vs 74% 47% vs 52%	0.12	No benefit of etoposide in HR patients
Euro-Ewing 99 ^[49]	Detailed in Table 2				

¹All chemotherapy regimens mentioned in the table is used in neoadjuvant setting followed-by local therapy (in terms of surgery and/or radiotherapy) followed by further adjuvant chemotherapy. EFS: Event free survival; EVAIA: Etoposide, vincristine, dactinomycin, ifosfamide, doxorubicin; HR: High risk; IE: Ifosfamide, etoposide; NS: Not significant; RFS: Relapse free survival; RT: Radiotherapy; SR: Standard risk; VAC: Vincristine, dactinomycin, cyclophosphamide; VACD: Vincristine, dactinomycin, cyclophosphamide, doxorubicin; VAIA: Vincristine, dactinomycin, ifosfamide, doxorubicin; VDC: Vincristine, doxorubicin, cyclophosphamide.

Table 2 Euro-Ewing 99 trial design and details

Randomized arm	Patients	n	Randomization	3-yr EFS
Arm 1	SR, Localized (good histologic response, < 200 mL + RT)	856	6#VIDE + 1#VAI f/b 7#VAI vs 7#VAC	78% vs 75%
Arm 2	HR, Localized (poor histologic response, ≥ 200 mL and RT alone)	---	6#VIDE + 1#VAI f/b 7#VAI vs BuMel (n = 281)	45% (BuMel)
	Lung metastasis only	---	6#VIDE + 1#VAI f/b 7#VAI + WLI vs BuMel	---
Arm 3	Extrapulmonary metastasis	---	6#VIDE + 1#VAI f/b BuMel/TreoMel vs clinical trial	---

BuMel: Busulphan and melphalan; EFS: Event free survival; f/b: Followed-by; HR: High risk; n: Number; RT: Radiotherapy; SR: Standard risk; TreoMel: TresoMelfalan and melphalan; VAC: Vincristine, dactinomycin, cyclophosphamide; VAI: Vincristine, dactinomycin, ifosfamide; VIDE: Vincristine, ifosfamide, doxorubicin, etoposide; WLI: Whole lung irradiation.

What local therapy and when?

The outcome of ESFT with surgery or radiotherapy alone was dismal and with introduction of polychemotherapy regimen improved the outcome dramatically by eradicating systemic micrometastasis in localized disease. But, chemotherapy alone can't eradicate ESF tumor cells and timely incorporation of local therapy either surgery and/or radiotherapy is crucial for optimum management and to produce high cure rate. The approach of local therapy evolved over time with better understanding of the disease biology, better radiation technique, invention of newer engineered prosthesis, better imaging modalities and more information of therapy related complications. The choice of local treatment influenced by multiple factors,

such as age of the patients, site and size of the tumor, local extent of the tumor, clinic-radiological response to chemotherapy, expertise and experience of the treating institution and surgeon and patient's choice, etc. The different modalities of local treatment include - surgery (amputation, limb salvage or organ sparing surgery) with or without adjuvant radiotherapy, radical radiotherapy, pre-operative radiotherapy, extracorporeal radiotherapy. No prospective formal comparison done between surgery and radiotherapy as local treatment. Across the clinical trials and institutional experience, surgery done better in terms of long term outcome (both local and systemic control), and thus a formal comparison between this two seems not feasible in future.

ESFT is a radiosensitive tumor, but the long term outcome was < 10% with high incidence of local^[36] and systemic recurrence. Surgery slowly replaced radiotherapy in view of better local control rate, lesser long-term complication compared to radiotherapy and with invention of better bone replacement materials (endoprosthesis, bone cement, allograft, vascularized autograft) the rate of limb sparing surgery has increased as a norm now-a-days^[36,37]. But, the surgery is also associated with long-term complications, such as post-op infection, limb-length discrepancy, fractures, etc. Maintaining limb length is difficult in growing children and expandable endoprosthesis comes handy in this scenario with its increasing uses.

The surgical resection principle depends on the respectability, size and sites the tumor and its operability after chemotherapy. A functional limb or organ is the norm after any local treatment modality. Amputation is rarely indicated and limb salvage or organ sparing surgery should be tried whenever feasible. Surgical resection should be tried whenever a marginal or wide resection is feasible as the outcome seems to be superior to radical radiotherapy as local control^[11,32,36,38-42]. Intralesional or debulking surgery should be avoided as the outcome is not superior over radiotherapy alone^[41].

Definitive or radical radiotherapy as local treatment modality used where non-mutilating, wide local excision is not feasible with a functional organ, more so in axial primary, such as - head and area, spine, pelvic primary and in very large lesion not amenable to curative surgery even after neoadjuvant chemotherapy, and in case of a metastatic disease, etc. The recommended dose varies from 55 to 60 Gy in standard fractionation with 2 cm margin that should include original biopsy scar^[39]. Care should be taken to avoid toxicity to adjacent normal organ and newer techniques, such as - intensity modulated radiotherapy, image guided planning or proton therapy, etc. should be used in more cases^[40]. Data on use of post-operative radiotherapy is mostly debated in view of conflicting results from observational studies^[41-43]. The only clear cut indication is that of intralesional surgery^[32] where further resection with remaining functional organ is not feasible. Many European institutions use adjuvant radiotherapy in patients with poor histologic response to chemotherapy (> 10% viable tumor cells) and in a soft tissue primary. Recent EE99 study also showed beneficial effect of adjuvant radiotherapy even in good responder and thus broadens its future use, though the risk-benefit ratio to be calculated stringently with long-term radiotherapy related complication. Pre-operative radiation therapy is a good viable future alternative where a complete resection looks not feasible after chemotherapy and thus can sterilize the compartment before reconsideration of surgery after radiotherapy, like in pelvic or spinal primary^[40].

What are the current and future studies?

Many collaborative studies are ongoing in ESFT to find out the most appropriate risk-stratified approach for

improving outcome with incorporation of high dose chemotherapy (Ewing 2008 and Italian ISG/AIEOP EW-1 study), introduction of metronomic chemotherapy as maintenance (COG AEWS1031 study), role of zoledronic acid (Ewing 2008 and Euro-Ewing 2012 study), optimum use of post-operative radiotherapy along with dose intensified approach (Euro-Ewing 2012 study), and comparison of vincristine, ifosfamide, doxorubicin and etoposide (VIDE) standard therapy in Europe vs VAC-IE (Euro-Ewing 2012 study).

METASTATIC DISEASE

Is site of metastasis prognostic?

ESFTs are an aggressive group of disease with high incidence of metastasis at presentation ranging from 20%-40% across different clinical trials and observation studies^[2,3,44-47]. Outcome of patients with lung metastasis was better as compared to those with bone metastasis or combined or to those with bone marrow involvement and single metastasis done better as compared to multiple metastases^[7]. The recent EE99 trial also revealed the presence and number of bone metastasis, presence and number of lung metastasis and bone marrow involvement as prognostic factors^[10]. More prospective studies are needed to define the prognostic nature of site and number of metastasis in a more stringent manner to tailor and intensify therapies.

Is the treatment same as localized disease?

The treatment protocol is similar like in those with localized disease with curative intent - neoadjuvant chemotherapy followed by institution of local therapy (surgery and/or radiotherapy) and further maintenance therapy or consolidation with high dose chemotherapy or an investigation novel agents/targeted therapy. Many agents in combination or with total body irradiation have been used as consolidation in metastatic disease. Definitive radiotherapy used more as compared to surgery in view of high residual disease at metastatic disease after neoadjuvant chemotherapy and a more conservative approach especially in those with disseminated metastases or with bone marrow involvement.

LOCAL TREATMENT: WHAT AND WHEN?

Local treatment usually incorporated after initial 5-6 cycles of chemotherapy and if there is good response to chemotherapy in both local site and metastatic site(s). WLI has been tried in clinical studies in patients with lung only metastasis^[48] with 5-year EFS up to 50% along with conventional chemotherapy compared to similar results with high dose chemotherapy without WLI^[8]. The EE99 study randomized (arm 2) patients with lung only metastasis VIDE chemotherapy followed by VAI as maintenance plus WLI vs BuMel based high dose chemotherapy as consolidation and the result is

pending^[49]. Local excision or radiation therapy has been tried in patients with bone metastases in retrospective studies with favorable outcome^[50]. Resection of pulmonary metastasis failed to show efficacy in two retrospective studies^[51,52] but require validation in a prospective manner especially in those with single lung metastasis.

WHAT IS THE ROLE OF HIGH DOSE CHEMOTHERAPY?

Dose intensity^[33] and high dose chemotherapy^[34,35] found to be effective and improved outcome in patients with localized disease especially in high risk disease. With the principle of dose intensity and dose density high dose chemotherapy with stem cell rescue has been tried in many randomized and non-randomized study to improve outcome in metastatic disease with mixed results. Single agent high dose melphalan failed to improve outcome^[53]. In a single arm study, BuMel conditioning in metastatic patients showed 5-year EFS of 52% in patients with lung metastasis and 36% in those with bone metastases^[8]. Subsequently many clinical trials have tried high dose chemotherapy in metastatic patients and showed mixed outcome as compared to conventional chemotherapy only (Table 3). Three large studies using high dose chemotherapy - the EE99 study randomized lung only metastatic group in to BuMel based high dose therapy vs WLI along with conventional chemotherapy after initial VIDE chemotherapy and the mature result is pending^[49]. The third arm randomized patients with extrapulmonary metastasis in BuMel or TreoMel based high dose chemotherapy vs investigational agent after standard VIDE based induction chemotherapy regimen and the early results showed 3-year overall survival^[10]. In study by Italian and Scandinavian sarcoma study group used BuMel conditioning with WLI in patients with lung only metastasis or single bone metastasis with 5-year EFS of 43%^[9]. The Ewing 2008 trial randomized patients with extrapulmonary metastasis after VAC chemotherapy to TreoMel based high dose chemotherapy vs continuation of VAC and the result is pending. On the contrary a study by Children's Cancer Group failed to show any improvement in outcome of patients with extrapulmonary metastases after VAC-IE based chemotherapy followed by high dose chemotherapy with melphalan, etoposide and total body irradiation^[54].

RELAPSED AND RECURRENT DISEASE

The progress of improved outcome in ESFT is attenuated by high incidence of recurrence (local and/or systemic) and remains the main challenge in multidisciplinary management of this aggressive malignancy, especially in those with metastatic disease. The incidence of local or distant relapse is approximately 20%-25% in the published literature^[45,55] and can reach up to 40% in metastatic setting^[2,47]. There is no standard established salvage therapy exist in recurrent disease with dismal

outcome of 20% in case of localized relapse^[56]. Few chemotherapy agents showed activity in recurrent disease with moderate but short lasting response rate - topotecan and cyclophosphamide^[57], ifosfamide in combination with carboplatin and etoposide^[58], irinotecan and temozolamide^[59]. Gemcitabine and docetaxel^[60] combination failed to show any clinically meaningful activity in recurrent ESFT. The mostly studied chemotherapeutic regimen in recurrent ESFT is of irinotecan and temozolamide from a phase 1 trial and from few institutional experiences^[61-65], like in other pediatric solid tumors. This combination used protracted course of irinotecan with synergistic activity of temozolamide and produced overall response rate of 25%-60% (Table 4). No prospective study to evaluate role of high dose chemotherapy has been done so far in recurrent ESFT and retrospective institutional data^[66,67] is available with modest activity. A well selected prospective trial in needed in this regards. The Euro-Ewing consortium started a randomized phase II/III four arm study (cyclophosphamide-topotecan vs gemcitabine-docetaxel vs high dose ifosfamide vs irinotecan-temozolamide) in recurrent ESFT and the trial will complete recruitment in 2019. A huge vacuum exist in effective salvage therapy of recurrent/refractory ESFT and novel targeted therapy is very much need to fill that unmet need. Future therapeutic trials will eye on combination of chemotherapy with targeted therapy in recurrent/refractory as well as metastatic disease.

NEW TARGETS AND TARGETED THERAPIES

With the plateau of survival with the current conventional chemotherapy and stem cell transplantation in metastatic and recurrent setting of ESFT the urgent need for novel targeted therapy should match the ongoing research in understanding the biology of ESFT with revelation of more and more oncologic pathways and targets. Various drugs has been discovered and tested in preclinical and clinical studies in ESFT by targeting EWS-FLI1 fusion protein, the hall mark of ESFT-CD99, angiogenic pathways (VEGF and its receptor), mammalian target of rapamycin (mTOR) and insulin-like growth factor-1 (IGF1) pathways, the osteoclastic-osteoblastic homeostasis and bone microenvironment, enzymatic pathways (poly ADP-ribose polymerase 1 - PARP1), and GD2 ganglioside pathways.

The mostly studied targeted therapy used in ESFT is by inhibiting EWS-FLI1 transcriptional complex. Many agents have been discovered that directly or indirectly inhibit EWS-FLI1 pathways - small-molecule YK-4-279 is in pre-clinical phase that directly inhibit interaction of EWS-FLI1 and RNA helicase A^[68], certain chemotherapy agents (doxorubicin, etoposide and cytarabine), midostaurin (broad spectrum protein kinase inhibitor)^[69], mithramycin (antibiotic inhibiting RNA synthesis)^[70], and the early clinical studies failed to show any clinical benefit of inhibiting EWS-FLI1 pathway in spite of being the

Table 3 Selected studies of high dose chemotherapy with stem cell rescue in Ewing sarcoma family tumors

Study (type)	Disease setting	n	Conditioning	Conclusion
CESS (retrospective) ^[78]	Recurrent or progressive disease (HDC after CR or PR)	73	BuMel (15) TreoMel (38) Other (20)	Early relapse - poor prognostic
Société Française des Cancers de l'Enfant (prospective) ^[8]	Metastatic at diagnosis	75	BuMel	Beneficial for lung only or bone metastases
Italian Sarcoma Group/Scandinavian Sarcoma Group IV Protocol (phase II) ^[9]	Metastatic at diagnosis (lung or single bone metastasis)	79	BuMel ± TBI	HDC with WLI is effective
Italian Sarcoma Group/Scandinavian Sarcoma Group III Protocol (prospective) ^[34]	High risk, localized	126	BuMel	Effective and feasible in patients with PR after chemotherapy
Euro-Ewing 99 (prospective) ^[10]	Metastatic at diagnosis	169	BuMel (123) Mel (15) Others (20)	Effective in Bone and Bone marrow metastases
EBMT registry (retrospective) ^[79]	Metastatic and HR, localized (n = 2411) Recurrent (n = 719)	3695	Heterogeneous regimens	Prognostic factors: Age, response to treatment, BuMel regimen

BuMel: Busulphan and melphalan; CR: Complete response; ESFT: Ewing sarcoma family of tumors; HDC: High dose chemotherapy; HR: High risk; n: Number; PR: Partial response; TBI: Total body irradiation; TreoMel: Treosulphan and melphalan; WLI: Whole lung irradiation.

Table 4 Data on Irinotecan-temozolamide salvage regimen in recurrent/refractory Ewing sarcoma family tumors

Ref.	n	Irinotecan schedule	ORR (n)	Toxicity (grade 3 and 4)
Kurucu <i>et al</i> ^[65]	20	20 mg/m ² (D1-5 and D8-D12)	55% (11)	Diarrhea - 9.2% Neutropenia - 11.3%
McNall-Knapp <i>et al</i> ^[64]	25	15 mg/m ² vs 20 mg/m ² (D1-5 and D8-D12) ¹	20% (5)	Diarrhea - 5%
Raciborska <i>et al</i> ^[63]	22	50 mg/m ² (D1-D5) ¹	50% (12)	Diarrhea - 15% Hematological - 10%
Wagner <i>et al</i> ^[62]	16	10-20 mg/m ² (D1-5 and D8-D12) - 3 weekly vs 4 weekly	25% (4)	Diarrhea - 11%
Casey <i>et al</i> ^[61]	20	20 mg/m ² (D1-5 and D8-D12)	63%	Diarrhea - 4.5% Hematological - 22%

¹With vincristine. ESFT: Ewing sarcoma family of tumors; n: Number; ORR: Overall response rate.

driver in ESFT carcinogenesis.

Anti-angiogenic approach has been used in recurrent tumors and thus inhibiting the tumor growth and its metastatic potential. Bevacizumab (monoclonal antibody against VEGFR) has been tested in phase II study by COG in combination with chemotherapy (vincristine, topotecan and cyclophosphamide) in recurrent setting with pending results (NCT00516295). Pazopanib (a small molecule multi-kinase inhibitor including VEGFR) has been tested in a phase I trial^[71] in refractory pediatric solid tumor and now being tested in a phase II study by COG that include ESFT and other sarcomas (NCT01956669). Regorafenib (a small molecule multi-kinase inhibitor like pazopanib) also being tested in refractory sarcomas including ESFT (NCT02048371).

ESFT is characterized by osteolytic bone lesion with extensive soft tissue component which is marked by osteoclastic activity and interaction between RANK and its ligand - RANKL^[72]. RANKL facilitates osteoclastic activity, with bone resorption and destruction, and tumor growth. Zoledronic acid, a bisphosphonate inhibit osteoclastic activity and its migration along with inhibition of RANK,

showed anti-tumor activity in *in-vivo* model of ESFT and the effect was accentuated by addition of ifosfamide^[73]. Ewing 2008 and Euro-Ewing 2012 trial is evaluating the benefit of zoledronic after combining with chemotherapy in localized ESFT.

IGF1 receptor (IGF1R) plays an important role downstream to EWS-FLI1 for cell survival, angiogenesis and metastasis. But, disappointing results with anti-IGF1R monoclonal antibody led to stoppage of further study of this novel agent due to dramatic but very short lasting response in refractory ESFTs. The cause of this early resistance is not fully understood though up-regulation of IGF1R or mTOR has been postulated^[74]. The COG future trial has planned combination of VAC-IE with anti-IGF1R antibody in metastatic disease to overcome this resistance.

The other potential targeted therapies include - PARP1 inhibitor olaparib in combination with temozolamide showed *in-vivo* and *in-vitro* activity^[75], anti-GD2 ganglioside (a neuroendocrine marker present in ESFT cells) chimeric antigen^[76], and anti-CD99 monoclonal antibody^[77] are in preclinical study periods.

FERTILITY ISSUE: A IMPORTANT BUT OFTEN IGNORED ISSUE

ESFT is a disease of young adolescent age group along with many patients in reproductive age group. All three treatment modality in ESFT affects gonadal and reproductive function in these patients. Multi-agent chemotherapy, especially with alkylators and anthracyclines, and radiotherapy are the two major culprits in this scenario due to their gonadotoxic effects. Many strategies have been taken to minimize or counter the gonadotoxic effects of cancer treatment especially with chemotherapy and radiotherapy.

Sperm cryopreservation is the standard and effective modality of fertility preservation in case of male patients, whenever indicated. Toxicity to ovarian follicle and embryo is a special scenario especially with pelvic radiotherapy. In a COG study^[78], 8.3% of female cancer survivors experienced acute ovarian failure, defined as loss of ovarian function with 5-years of cancer diagnosis. Radiotherapy toxicity to ovary depends on age of the patients, concurrent ovariotoxic chemotherapy, dose and fractionation of radiotherapy and volume of radiation field. Cost, experience, expertise, infrastructure and low success rate are the main logistic issue in female fertility preservation.

Embryo cryopreservation is an option for fertility preservation in female patients with a male partner, whereas cryopreservation of mature or immature oocytes is a viable option for those refuse to opt for a sperm donor. Cumulative pregnancy rate up to 40% has been reported with the former technique^[79] but with a modest success with the later technique^[80]. Cryopreservation of ovarian tissue is the only measures of fertility preservation in very young girls, and recent reports of successful pregnancy have been described in literature^[81,82].

Ovarian transposition or ovariopexy is the method to preserve ovarian function in patients receiving pelvic radiotherapy but high rate of permanent cessation of ovarian function has been reported in earlier series^[83]. Intensity modulated radiotherapy or 3-D conformal CT planning in radiotherapy can minimize the gonadal toxicity in case of very small pelvic tumor or a tumor distant to ovary.

Protective role of concurrent GnRH-a has been described in literature during combination gonadotoxic chemotherapy. In study of lymphoma patients aged 15-40 years, GnRH-a group resumed menstruation in 93.7% cases within 3-8 mo of chemotherapy as compared to 39% in historical controls of same disease group who didn't received GnRH-a^[84]. In important issue remains in fertility preservation where the ovary itself is the primary site of disease in ESFT and rarely ESFT can metastasize to the ovary^[85-87].

CONCLUSION

ESFTs are a rare aggressive tumor with high rate of

metastasis at presentation and high incidence of recurrence. The outcome of those with localized improved to 70% after multimodality approach mainly by better understanding of disease biology, risk adapted chemotherapeutic approach, timely incorporation of local therapy, and improvement in technology. But, the outcome of those with metastatic and recurrent disease is dismal and no significant advancement has been made in these patients to improve outcome in last four decades. The overall improvement in outcome of ESFT has been made through the tremendous efforts of researcher, clinicians all over the world, better liaison between all the stakeholders of treating team, and collaborative international research in a huge number of cases. The main challenge now remains in preventing recurrence, preventing drug resistance, reducing therapy related long-term toxicities and improving outcome in those with metastatic and relapsed/recurrent disease. No potential biomarker has been identified so far to predict therapeutic efficacy of chemotherapeutic agents and predicting recurrences. The future hope lies in finding useful biomarker, better understanding of disease biology and chemotherapy resistance of ESFT cells, proper designing and execution of targeted therapies currently going under clinical trials, better use of high throughput method to detect novel driver mutations/pathways and potential targets. Better selection of risk group and designing of trials combining chemotherapeutic agents with targeted therapies to bypass drug resistance along with judicious use of high dose chemotherapies, selection of more non-toxic agents with high efficacy and broad therapeutic windows will help to improve future outcomes in expense of decreased treatment related long-term toxicities and good quality of life in survivors.

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