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NARRATIVE REVIEW

EWING SARCOMA: A REAPPRAISAL

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ABSTRACT: Ewing sarcoma (ES) is an aggressive sarcoma of bone and soft tissues arising predominantly in children and young adults. Current management of primary ES relies on a multimodality approach, coupling intensive cytotoxic drugs regimens with surgery and/or radiotherapy. The combination of primary site control and possible metastatic disease resulted in increased survival rates in localized disease, at the expense of substantial acute and long-term toxicity. Contrarily, the prognosis is still dismal in the metastatic setting, especially for patients with recurrent ES. Indeed, the lack of an effective treatment strategy after a first-line chemotherapy represents an unmet clinical need. The aim of this study is to examine the current treatment options and discuss potential future perspectives that could answer to the key issues in the management of ES.

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Impact statement: This study reports the current management of Ewing sarcoma on a multimodal approach, coupling intensive cytotoxic drugs regimens with surgery and/or radiotherapy. It examines the current options and discuss potential future prospective.

Key words: *Ewing's sarcoma; sequential therapy; multidisciplinarity; new perspectives.*

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INTRODUCTION

ES is a rare tumor developed in bone and in soft tissue. The incidence ranges from 0,1-1 cases/million. The peak of incidence is between infancy and early adulthood (5-24 years old) (1-4). However, adults and elderly people can also be affected, mainly in extraosseous tissues. ES is considered in most situation a systemic disease from the beginning (5, 6) which, in absence of therapy, lead the patient to death in 90% of cases for metastatic disease. Despite multimodal and multidisciplinary approaches, metastatic disease occurs in 30% of the patients predominantly in the lungs (70-80%), bone marrow and bone (45-49%), soft tissue, liver, and brain (5-8). The cell of origin of ES is not well recognized, however the mesenchymal stem cell is the most accepted between geneticist and pathologists (9-14).

The most important molecular event in ES's cells is the chromosomal translocation between ETS and FET genes, with a reciprocal translocation (t 11;22) (q24; q12). The result is EWS/FLI 1 oncogenic gene fusion (15, 16). The product of EWS/FLI 1 gene fusion leads to gene regulation with activation and repression of thousands of other genes (15-18).
Other chromosomal variant is copying member variation and point mutations (STAG2, TP53, Rb1) but their real meaning is not definitively known (15, 19, 20) (**Table 1**).
The 2020 World Health Organization (WHO) classification of sarcomas calls "Ewing Sarcoma Family" the same nosological entity with similar morphological aspects, but with multiple chromosomal abnormalities: they have different prognosis and

Table 1. *Genes and genes variation related to ES.*

	GENES	FUSION PROTEINS	PREVALENCE
EWING sarcoma	FET-ETS	EWSR1-FLI1	85%
		EWSR1-ERG	10%
		EWSR1-FEV	<1%
		EWR1-ETV1	<1%
		EWSR1-ETV4	<1%
Ewing like sarcoma	FET (no ETS)	EWSR1-SP3	<1%
		EWSR1-PATZ1	<1%
		EWSR1-SMARCA5	<1%
		EWSR1-POU5F1	<1%
		EWSR1-NFATc2	<1%
		FUS-NFATc2	<1%
Ewing like sarcoma	no FET	BCOR / $CCNB_3$	<1%
		BCOR / $MAML_3$	<1%
		BCOR / ITD_5	<1%
		ZC3H7B-BCOR	<1%
		CIC / $FOXO_4$	<1%
		CIC / DUX_4	<1%
Atypical Ewing sarcoma	FET-ETS	FUS-ERG	<1%
		FUS-FEV	<1%

susceptibility to the therapy (see **Table 1**) (15, 16). Although ES is a high-grade tumor, it is characterized by low mutational burden. This is of fundamental importance in the therapeutic strategy.

GENERAL CONSIDERATION IN THERAPY

In case of osseous or extraosseous mass, a plain X ray of the segment, followed by CT scan and/ or MRI of the anatomical area is recommended. If the suspicion is confirmed a tru-cut or an incisional biopsy is mandatory. If ES diagnosis is confirmed a complete disease staging with whole body CT scan, PET CT scan is required. Some protocols suggest bone marrow biopsy to exclude bone marrow dissemination.

ES family recognize a localized in confront with a disseminated, metastatic disease. All decision about the ES therapeutic management should be taken in a multidisciplinary multitask group including at least Radiologist, Pathologist, Orthopedic, Surgeon, Radiotherapist and Oncologist (16, 21, 22).

The prognosis of the localized disease is determined by many factors: age and Performance Status of the patient, tumor volume (>200 ml), tumor site (better in the acral part of the skeleton than in the axial part; better osseous than extraosseous) (16, 22).

Following the guidelines (16, 22) in localized ES the most effective strategy involves a general approach with chemotherapy to reduce both the volume of the primary tumor and the risk of micrometastasis.

The local phase include surgery -± radiotherapy. Surgery is the preferred approach and leads to a higher local control of the disease. The surgical margin is a fundamental marker of radicality. Margins must be wide enough for oncological control but must respect the function either in osseous or in extraosseous ES (22, 23). Despite ES radiosensitivity, radiotherapy as unique modality of local treatment results in a high incidence of local recurrence and an increased risk of long-term toxicity (secondary bone tumor, osteoporosis, bone fractures).

An exclusive radiotherapy treatment can be considered in non-operable disease: large volume (>200 ml), pelvic or spine localization, poor histological response to neoadjuvant chemotherapy or extraosseous localization. The recommended dose is 54-55 Gy to the tumor in fractionated schedule (24-27). Proton beam therapy is a new radiotherapy technique that seems to increase the percentage of local control and reduce the risk of toxicity, particularly in the youngest patients, but more data on proton therapy compared with traditional radiotherapy are needed (22, 28).

As demonstrated by many studies (16, 22, 29) perioperative chemotherapy with neoadjuvant and adjuvant approach is strongly suggested. Before 1980 ES was treated solely with surgery and radiotherapy and about 95% of the patients died from disease (30). The neoadjuvant/adjuvant strategy has a double end point: better local control and reduction of metastatic relapse.

With the combination including Vincristine, Doxorubicin, Ciclophosphamide, (VDC) ± Ifosfamide and Etoposide, five years overall survival in localized disease increased from zero to 50-80% (31-33). The addition of Ifosfamide and Etoposide (EI) to VDC regime increased 5 years survival to 60-70% always in localized disease (34-38). Some recent European trials assessed efficacy and safety of other regimens such as VIDE (Vincristine, Ifosfamide, Doxorubicin and Etoposide) as induction therapy followed by VAI (Vincristine, Actinomycin D, Ifosfamide) or VAC (Vincristine, Actinomycin D, cyclophosphamide) as consolidation (see **Figure 1**) (39). Some attempts were done with dose density schedule recycling every 14 days. A higher percentage of local response were recorded, but with a very high level of toxicities.

Similarly high-dose chemotherapy with bone marrow or stem cell transplant did not increase the percentage of event free survival (EFS).

In conclusion the duration of chemotherapy (at least 30 weeks) is more important than the dose intensity or dose density (40). In **Table 2** we resume the most common sequences in ES trials.

METASTATIC DISEASE

The prognosis of refractory disease (less than 90% of tumor necrosis after chemotherapy in local disease) or recurrent/metastatic ES remains very severe. The 5 years survival is 22% for recurrent ES and is less than 10% for metastatic disease.

Two different population are recognized:

1. poor responders to chemotherapy after local treatment (<90% necrosis).
2. de novo metastatic disease or relapse.

To date no standard treatment has been defined for metastatic disease and the role of surgery in local relapse or limited pulmonary metastasis (1-2 nodules) is not completely understood.

Many combinations including drugs not used in neoadjuvant/adjuvant setting are proposed: Temozolomide + Irinotecan (46), Topotecan + Ciclophosfamide (47), Docetaxel + Gemcitabine (48), High-dose Ifosfamide (49).

All these drugs have been evaluated in phase II trials and only once comparative study is available (49).

Objective responses range from 0 to 60 % but they don't translate into a longer survival, especially for

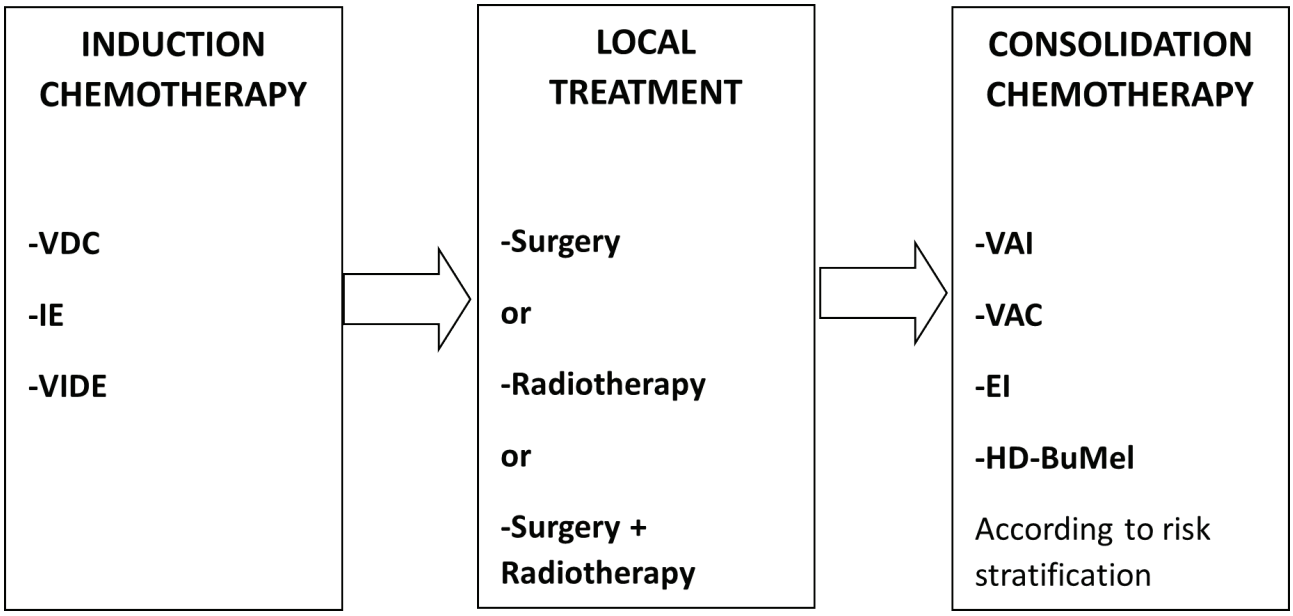

Figure 1. *Sequential therapy in localized ES.*
Abbreviations: VDC: Vincristine/Doxorubicin/Cyclophosphamide; IE: Ifosfamide/Etoposide; VIDE: Vincristine/Ifosfamide/Doxorubicin/Etoposide; VAI: Vincristine/Actinomycin D/Ifosfamide; VAC: Vincristine/Actinomycin D/Cyclophosphamide; HD-BuMel: High Dose Busulfan/Melphalan and Stem Cell Rescue.

Table 2. *The most important trials in localized ES treatment.*

AUTHOR/TRIAL NAME	YEAR	CHEMOTHERAPY	RESULTS
Grier/INT-0091 (41)	2003	VDC *vs*. VDC/IE	5 y EFS 54% *vs*. 69% with addition of IE in localized ES
Kolb/MSK (42)	2003	VDC/IE with augmented Cyclophosphamide	4 y EFS 82% in localized ES
Granowetter/INT-0154 (43)	2009	VDC/IE with augmented alkylating doses vs standard VDC/IE	No improvement in outcomes with augmented doses
Womer/AEWS0031 (44)	2012	cVDC/IE	6 y EFS improved to 73% from 65% with compressed chemotherapy for localized ES
Dirksen/Euro-E.W.I.N.G.99 and Ewing 2008 (45)	2019	VAI vs VAI/HD-Bu-Mel	No clear benefit from BuMel in high-risk ES
Brennan/Euro Ewing 2012 (29)	2022	VIDE induction +VAI/VAC (or VIA/HD-BuMel) *vs*. VDC/IE induction + IE/VC (or VAI/HD-BuMel)	3 y EFS 67% *vs*. 61% in the VDC/IE induction group

Abbreviations: VDC: Vincristine/Doxorubicin/Cyclophosphamide; IE: Ifosfamide/Etoposide; cVDC: compressed VDC; VAI: Vincristine/Actinomycin D/Ifosfamide; HD-BuMel: High Dose Busulfan/Melphalan and Stem Cell Rescue; VIDE: Vincristine/Ifosfamide/Doxorubicin/Etoposide; VAC: Vincristine/Actinomycin D/Cyclophosphamide.

early recurrences (<2 years from the end of adjuvant chemotherapy). A group apart is the solitary lung metastasis that removed can guarantee 5 years survival in the 30% of patients.

The European study rEECur (49) with multistage design comparing Temozolomide + Irinotecan, Topotecan + Ciclophosfamide, High-dose Ifosfamide and Docetaxel + Gemcitabine showed that High-dose Ifosfamide is the most effective treatment in Overall Survival (OS). Sites of recurrences were replapsed in the primary site (15%), pleuropulmonary (34%), another site or multiple (51%). High-dose Ifosfamide did better: EFS 5.7 months and OS 16.8 months were the results. Better survival was recorded in teens <14 years old.

NON-CHEMOTHERAPY DRUGS

At present no target therapies are recognized as part of active treatment in relapsed ES.

Cabozantinib 40 mg/m^2 in children and 60 mg/m^2 in adults was investigated in a French study (57). This drug is MET and VEGFR$_2$ inhibitor, two products of oncogene demonstrated in ES cancerogenesis.

Forty-five patients with relapsed/pre-treated ES were recruited. Ten patients had PR (25.6%) and 13 (38.4%) SD.

At 6 month follow up 25.6% of patients were progression free. Neutropenia, hand and foot syndrome, transaminases increase was recorded. Despite the positive results of this study Cabozantinib is not approved by European Medicine Agency (EMA) in pre-treated ES (**Tables 3, 4**).

IMMUNOTHERAPY

In such distressing panorama many efforts have been made for the implementation of immunotherapy in relapsed or metastatic ES. However, check point inhibitors (ICIs) (anti PD1, anti PDL1 and anti CLTA4) offered very poor results.

Tawbi (58) *et al*. in their study did not record any objective response. Few trials are still on going with different ICIs than Nivolumab.

Some T-cell based therapies are investigated in Clinical Trials against cell surface target as EGFR, HER$_2$, ROR$_1$, IGF$_1$R. To date, no drug has been approved for relapsed ES (**Table 3**).

INVESTIGATIONAL APPROCHES

The rationale for experimental alternative treatment is based on ES molecular pathogenesis, particularly on the implication of a unique molecular driver in cell transformation. The target inhibition of EWS-FLI1 has been showing promising results in a phase I/II trial investigating the molecule YK-4-279 (TK216), designed to bind ETS proteins directly, disrupt protein interactions, inhibit

Table 3. *Target therapy drugs.*

TARGET	DRUG
CD-99	Anti CD-99 mAb
PARP	PARP INHIBITORS
GD2	CAR anti GD2
VEGFR	Bevacizumab
IGF1R	Anti IGF1R
RANK	Zoledronic acid

Table 4. *Principal drug cited in different study to treat ES with results.*

DRUG	AUTHOR-YEAR	RESULTS
Figitumumab	Olmos-2010 (50)	2/16 PR
Figitumumab	Juergens-2011 (51)	14% ORR
R1507 anti IGF1R	Pappo-2011 (52)	10% ORR
Ganitumab	Tap-2012 (53)	6% ORR
Olaparib	Choy-2014 (54)	No ORR
Talazoparib + Temozolamide	Schafer-2020 (55)	No ORR
Talazoparib + Irinotecan ± Temozolamide	Federico-2020 (56)	1 CR – 4 PR
Cabozantinib	Italiano-2020 (57)	26% ORR

transcription factor function, and cause apoptotic cell death (59). Yet, the development of drug resistance through clonal selection is inevitable, theoretically limiting its long-term efficacy (60). In this context, preclinical data showed that cancer stem cells plasticity and tumor heterogeneity can be reverted by correcting the defective TARBP2-dependent microRNA maturation by exposure to the fluoroquinolone enoxacin (61). Riggi *et al*. in their recent study explored the potentially targeted molecular and epigenetic mechanism by which EWS and its partners promote cell transformation (62). The modification of chromatin structure and DNA accessibility to transcription factors seems to play a major role. EWS-FLI1 controls the epigenetic regulation of gene expression through different molecular pathway: the recruitment of the major ATP-dependent chromatin-remodeling complex SWI/SNF (switch/sucrose non-fragmentable), also known as BAF (BRG1/BRM-associated factor), which allows DNA accessibility; the reduction of DNA methylation and the inhibition of microRNAs that promotes differentiation (63). The encouraging data on the activity of KDM1A, a demethylase identified to regulated chromatin states through the removal of mono- and dimethyl group, from in vitro studies led to the active development of several small-molecule KDM1A inhibitors in different solid and hematological tumors (64). As KDM1A is overexpressed in ES tumors, directed KDM1A inhibition was first tested in vitro with the use of non-competitive KDM1A inhibitor SP-2509, showing a dramatic reversal of both the up- and downregulated transcriptional profiles of EWS/FLI and EWS/ERG accompanied by the induction of apoptosis and disruption of morphologic and oncogenic phenotypes modulated by EWS/FLI (65, 66). This evidence opened the door to dedicated currently ongoing Clinical Trial. A phase II Trial was designed to test the activity of the IGF-R targeted monoclonal antibody R1507 in patients with recurrent of refractory sarcomas. Although IGFR signaling pathway is implicated in the transformation of fibroblast and is known to support EWS/ETS-driven oncogenesis, its inhibition led to disappointed results (67, 68). Poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) have been showing considerable efficacy in different clinical settings, especially in in tumors with homologous recombination deficiency. The high expression of PARP in ES cells led to test PARPi in clinic with scarce results with Olaparib. Trial testing the combination of chemotherapy with PARPi are still ongoing (69). Finally, encouraging early phase data comes from the innovative field of the Chimeric Antigen Receptor (CAR) cells therapies (70). In **Table 4** are resumed some of these studies.

CONCLUSIONS

To date, polychemotherapy remains the cornerstone treatment for ES both in local and metastatic/relapsed disease. The multidisciplinary approach has significantly improved OS for localized disease, with 60-70% 5 years survival using neoadjuvant/adjuvant therapies associated with surgery and or radiotherapy. On the contrary, despite the multimodal treatment, survival in metastatic disease is less than 10% at 3 years.
Characteristically ES is recognized for a specific translocation EWSR1 on chromosome 22 to site 1 gene (FLI1) on chromosome 11: the fusion EWS/FLI1 is fundamental for tumorigenesis in ES and theoretically it could be a specific target for a future effective therapy. Unfortunately, neither this specific translocation nor different mutations seems to be a reliable target for therapies. A great effort is required in ES, as well in other bone and STS, to identify the cell of origin, different and druggable molecular activities, not only in "time" ES but also in every subtype of round cell sarcomas family. Within the same morphological aspect multiple entities with different biological and clinical behavior have been recently described, and treatment strategies should be increasingly targeted. The ancient chemotherapy regimens included in VCD ± EI combination has allowed a great deal in localized disease, but the substantial toxicity of the standard therapies and the limited options for patients with recurred ES still represent an unmet need.

COMPLIANCE WITH ETHICAL STANDARDS

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The Authors have declared no conflict of interests.

Availability of data and materials

The data underlying this article are available in the article.

Authors' contributions

The Authors contributed equally to the conception of the article.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Publication ethics

Plagiarism

This is a review article and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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