Ewing Sarcoma

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INTRODUCTION

The Ewing sarcoma (EWS) family of tumors is a group of tumors consisting of typical EWS, extraosseous EWS, atypical EWS, primitive neuroectodermal tumor (PNET), and Askin tumor. The unifying feature of these tumors is the specific chromosomal translocation fusing the *EWS* gene to a subset of ETS transcription factor family members, most commonly the *FLI1* gene (less frequently, *ERG*, *ETV1*, *E1A-F*, or *FEV*). The peak incidence of EWS is during adolescence. Treatment of these tumors requires a multidisciplinary approach. The ideal team consists of experienced oncologists, orthopedists, radiation oncologists, radiologists, pathologists, and supportive care members. Despite extensive research leading to the finding of the disease-defining translocations, our understanding of the biology and its clinical correlation is still limited and there has been little progress in our ability to cure this disease in the past 30 years. Given the lack of recent clinical progress, optimal management of these patients by experienced teams is of particular importance. There have not been major advances in survival in patients with metastatic disease since standard use of adjuvant chemotherapy was adopted in the 1970s. Therefore, it is imperative to continue developing clinical trials and encouraging enrollment into these studies. This chapter will discuss the current approach to diagnosis and management for those with the EWS family of tumors.

EPIDEMIOLOGY

EWS is the second most common primary bone malignancy of childhood and young adulthood. About 80% of EWS occurs in patients younger than 20 years at the time of diagnosis.¹ The annual incidence of EWS in this population is approximately 2.9 cases per million.² The incidence is slightly higher in males than females at a ratio of 1.2:1. The most striking epidemiologic feature of EWS is the difference in racial distribution. It occurs more frequently in Caucasians, with a lower occurrence rate in people of Asian and African American (AA) descent.^{1,2} Worch et al. looked at the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2005 and found that the racial distribution of EWS was 78.6% white non-Hispanic, 14% Hispanic, 4.9% Asian, and 2.5% AA.³ This indicates lower occurrence in people of AA descent, as this group makes up about 13% of the population. This racial difference is seen at every age, and the explanation has yet to be fully elucidated. Beck et al., looking at the different length polymorphisms of the *NR0B1* and *CAV1* GGAA microsatellite in both European and African populations, were able to demonstrate that the number of GGAA microsatellite repeats is considerably higher in African populations, as a possible explanation.⁴ Additional research is needed to look into these racial differences and the correlation of the GGAA microsatellite repeats.

CLINICAL PRESENTATION

The presenting symptoms for EWS depend on the location of the tumor. When presenting in the bone, pain is a common presenting symptom, though a painless mass is not uncommon. When the initial site is in the soft tissue, the patient will often present with a mass, which may or may not be painful. Given that the primary incidence is in adolescence, pain is often mistaken for so-called “growing pains.” It is not uncommon for it to take weeks to months from the onset of symptoms for a diagnosis of EWS. EWS most often arises in the bones (85%), with the remaining 15% occurring in soft tissues.² Additional presenting symptoms may include local swelling, pathologic fractures, and systemic symptoms such

as fever and weight loss. EWS can be found in almost any bone or soft tissue. Approximately 38% of EWS appears at the diaphysis of the long bone in the extremities. EWS can present at the flat bones of the axial skeleton, such as the ribs and pelvis, at about 27%.² Although extremity lesions are still more common, central lesions are seen in EWS more frequently. EWS that arises from the bone can also have a relatively large soft tissue component, especially when compared to osteosarcoma.

There are no specific laboratory findings or tumor markers associated with EWS. Nonspecific findings such as an elevated serum lactate dehydrogenase (LDH) and alkaline phosphatase are seen with increased tumor burden, cell turnover, and bone destruction. Van Maldegem et al. completed a meta-analysis looking at possible biomarkers as prognostic factors.¹⁰ It was thought that LDH was a prognostic marker, but has been shadowed by the prognostic impact of metastatic disease, which clearly has the most impact on overall survival (OS). Decreases in white blood cells, hemoglobin, and platelets are not typically seen in EWS, unless there is significant bone marrow involvement.

DIAGNOSTIC APPROACH

Tissue diagnosis by an experienced pathologist is essential. Upfront resection of these tumors is not typically attempted in preference of biopsy, whether by percutaneous core-needle biopsy or via an open surgical procedure (Figure 14.1). The most common approach is to defer complete surgical

FIGURE 14.1 Workup for newly suspected bone sarcoma.

CBC, complete blood count; CMP, complete metabolic panel; GFR, glomerular filtration rate; LDH, lactate dehydrogenase.

Source: With permission from Reed DR, Hayashi M, Wagner L, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. *Cancer*. 2017;123(12):2206–2218. doi: 10.1002/cncr.30589.

resection until after the patient has received neoadjuvant chemotherapy. This has multiple benefits including allowing time for preparation for the surgery and obtaining custom prostheses if needed. Neoadjuvant chemotherapy typically also reduces the size of the tumor, which may facilitate surgical resection. Finally, neoadjuvant chemotherapy allows for immediate systemic therapy to treat/prevent the development of macroscopic and microscopic metastases.

Core-needle biopsy with image guidance can provide sufficient samples for diagnosis and, being less invasive, is the preferred initial biopsy technique.² In rare cases, a core-needle biopsy does not provide enough tissue for diagnosis and a repeat or open biopsy must be attempted. It is imperative to minimize the tissue contamination from needle or open biopsy. The biopsy tract should be excised at the time of definitive surgery; hence, discussion with an experienced orthopedic oncologist on biopsy location is critical. If possible, the same surgical team performing the definitive surgery should obtain the biopsy or be consulted about the optimal image-guided core biopsy approach.

Radiographic Features (Prior to Biopsy)

At the time of diagnosis, a plain radiograph of the affected bone is done in addition to cross-sectional imaging, such as MRI or CT. In EWS, there will typically be x-ray findings in the diaphysis of the long bones that extend toward the metaphysis. The classic “onion skin” appearance of EWS is a lamellated periosteal reaction. It is seen in about 23% of presentations.¹ More common nonspecific features seen on x-ray image include lytic lesions (75%), soft tissue extension (64%), and reactive bone formation (25%).¹ Less common findings include radiating spicules, a.k.a. “sunburst appearance” (20%); periosteal thickening (19%); sclerosis (16%); and fracture (13%). The aforementioned sunburst appearance is more classically associated with osteosarcoma; however, it can be seen in both. The major difference between images of osteosarcoma and EWS is the location, which is typically at the metaphysis for osteosarcoma and diaphysis for EWS.¹ Those with soft tissue EWS may have normal x-ray imaging, unless there is bony erosion or the soft tissue mass is large enough to be radiopaque. Once the initial x-ray study is completed, additional imaging is mandated as part of the workup. More detailed imaging of the primary site is needed using MRI with gadolinium contrast agent. This provides the resolution needed for proper surgical mapping prior to the biopsy and definitive surgery. In addition, a CT scan of the chest is required to assess for metastatic disease to the lungs, as it is the most common site for metastasis. Typically, a CT scan of the chest without intravenous (IV) contrast is sufficient, as the air provides the “contrast” needed when looking for metastatic tissue in the lungs; however, contrast may be needed if assessing the soft tissue component of an EWS involving the chest. Historically, technetium bone scan was used to assess for local and metastatic bone disease. The advantage to the bone scan is that it is cheaper and involves less radiation. However, more recently, there has been a shift to the fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) as it is more sensitive for metastatic disease in EWS and can help assess nonskeletal lesions.^{2,5}

MOLECULAR BIOLOGY

The pathognomonic molecular finding in EWS family tumors is a reciprocal chromosomal translocation, most commonly occurring between the chromosomes 11 and 22. More specifically, t(11;22)(q24;q12) occurs in about 85% of cases. The gene name for the chromosome 22 translocation partner is *EWSR1*, and the gene name for the chromosome 11 partner is *FLI1*. The presence of this fusion protein correlates with a high expression of cell surface sialoglycoprotein CD99.² Of the 15% of EWSs that do not harbor the *EWSR1-FLI1* translocation, these tumors typically have evidence for gene rearrangements for *EWSR1* to a different fusion partner, the most common being *ERG* on chromosome 21q22, which is seen in about 10% of EWS family tumors. Other less frequent fusion partners seen in less than 1% of cases include *ETV1* on chromosome 7p22, *ETV4* on chromosome 17q12, and *FEV* on chromosome 2q33. In addition to *EWSR1*-associated translocations, other chromosomal changes can also be simultaneously present. Trisomy 8 and 12 are observed in 50% and 33% of cases, respectively.² Structural changes at chromosomes 1 and 16 are observed in about 20% of cases, typically leading to the gain of 1q, a loss of 16q, or the formation of a derivative chromosome der(1;16). There have been some reports describing fusions between *FUS* and either *ERG* or *FEV* in EWS. The *FUS* protein is highly related to *EWS*. The clinical significance of these various translocation partners to *EWSR1*, along with the other structural chromosomal changes, is unknown at this time. Additional research is needed to determine their significance.

It is believed that a second mutational event is needed to immortalize these *EWS-FLI1*-expressing cells. It was initially thought that p53 pathway was involved, but aberrations in p53 are relatively rare

in EWS, occurring in less than 15% of tumors. Some preclinical data suggest that NOTCH signaling or insulin-like growth factor 1 receptor (IGF1R) circuit is involved.²

There is no conclusive evidence that any of these varying aberrations, such as the varying translocation partners with *EWSR1*, such as *FLI1*, *ERG*, *ETV1*, *E1A-F*, or *FEV* gene, play a role in a clinically meaningful way in regard to prognosis. Currently, the main prognostic factor remains the presence or absence of metastatic disease. It is important to acknowledge that in Europe, they also look at the response to neoadjuvant chemotherapy, which at the time of writing this chapter had not yet been incorporated in North American protocols.

THERAPEUTIC APPROACH

EWS requires a multidisciplinary team approach to treatment, including orthopedic oncology, interventional radiology, radiation oncology, radiology, and medical/pediatric oncology (see Figure 14.2). A specialized orthopedic oncologist can take care of the biopsy and the surgical resection of the primary tumor. The biopsy could also be completed by interventional radiology with consultation of the primary surgical team to identify the proper approach to ensure removal of the biopsy tract when the patient undergoes definitive surgical resection of the primary tumor. Radiation oncology is involved to provide radiation for local control of the primary tumor site when needed if complete surgical resection is not possible, the patient is not a surgical candidate, the patient declines surgery, or there are positive margins after surgical resection. A pediatric or medical oncologist is involved to administer systemic chemotherapy. When available, patients should be encouraged to participate in clinical trials to further advance our treatment strategies and potentially receive improved treatment. Neoadjuvant chemotherapy should be initiated quickly after completing histologic confirmation of the diagnosis, metastatic workup, and baseline assessment.

The use of chemotherapy to treat EWS started only in the 1960s. It was Sutow and Sullivan who, in 1962, published a report on cyclophosphamide to treat EWS.¹¹ In 1974, Rosen et al. from Memorial Sloan Kettering first started treating EWS with multiple agents together, as is currently done.¹² Their initial regimen consisted of vincristine, cyclophosphamide, actinomycin D, and doxorubicin (VACD). Chemotherapy greatly improved the outcomes of patients with EWS. The first cooperative study by Intergroup Ewing's Sarcoma Study (IESS) from 1973 to 1978 showed that the addition of doxorubicin to VAC had a 5-year OS rate of about 60%, which was compared to 24% with VAC alone.⁶ The American Intergroup Ewing's trial (INT-0091/POG-8850/CCG7881) determined that the addition of ifosfamide and etoposide (IE) to VACD improved the event-free survival (EFS) rate to 69% in those with localized disease.⁶ There was, however, no benefit in metastatic disease.

The combination of cooperative groups in North America has allowed for increased enrollment of patients with this rare tumor into therapeutic clinical trials. The Children's Oncology Group (COG) is one of the leading cooperative groups in pediatric oncology in North America. The COG trial AEWS0031 demonstrated improved survival in EWS patients with localized disease when treated with an interval-compressed version of VDC/IE given every 2 weeks instead of every 3 weeks. In Europe, a different standard regimen of VIDE is used, which consists of vincristine, ifosfamide, doxorubicin, and etoposide.⁵ The Euro-E.W.I.N.G. 99 clinical trial looked at the safety of treating with VIDE, compared to earlier standard of vincristine, actinomycin D, and cyclophosphamide (VAC) or vincristine, actinomycin D, and ifosfamide (VAI) in Europe. It demonstrated tolerance and efficacy, and thus, the Europeans now treat with VIDE (vincristine 1.5 mg/m² × 1 day, ifosfamide 3 g/m² × 3 days, doxorubicin 20 mg/m² × 3 days, and etoposide 150 mg/m² × 3 days). Currently, an ongoing Euro-Ewing 12 study (EudraCT number 2012-002107-17) is being conducted which looks at a direct comparison of VIDE and VDC/IE. Historically, the outcomes have been comparable between regimens; however, only now are they being compared head to head.

The therapeutic regimen used in North America consists of vincristine (1.5 mg/m², on day 1), doxorubicin (75 mg/m² on days 1 and 2), cyclophosphamide (1,200 mg/m² on day 1) alternating every 2 weeks with ifosfamide (1,800 mg/m² on days 1–5) and etoposide (100 mg/m² on days 1–5). This is referred to as VDC/IE and is considered the current standard of care for a pediatric oncologist in North America. It currently consists of 12 weeks of neoadjuvant chemotherapy, followed by local control with surgery and/or radiation and then an additional 16 weeks of adjuvant chemotherapy for a total of 28 weeks of therapy.

While most pediatric oncologists follow the COG regimen described above, adult medical oncologists treat with different protocols. As demonstrated in the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2019, the possible regimens medical oncologists use to treat localized EWS are: VDC/IE (same as pediatrics), VDI (vincristine 2 mg/m², doxorubicin 75 mg/m², and

FIGURE 14.2 Pathway for treating newly diagnosed and relapsed Ewing sarcoma.

CR, complete response; IE, ifosfamide and etoposide; PD, progressive disease; PR, partial response; SD, stable disease; VDC, vincristine, doxorubicin, and cyclophosphamide; XRT, x-ray therapy.

Source: Used with permission from Reed DR, Hayashi M, Wagner L, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. *Cancer*. 2017;123(12):2206–2218. doi:10.1002/cncr.30589.

ifosfamide 10 g/m²), and VIDE. When treating metastatic disease, they use the same three regimens plus the additional option of VDC alone.

The choice of local control is dependent on the location of the tumor and the ability to obtain negative surgical margins. Surgical resection is preferred if negative margins are obtainable and the associated morbidity is not extreme. The use of radiation can provide an acceptable alternative to surgery for local control when negative margins are not obtainable and surgical morbidity is great.

Debulking operations that leave gross residual tumor are never indicated as they will just delay chemotherapy and the patient would require full-dose radiation therapy (RT) to treat gross residual disease, the same as if the surgery did not occur. A 2015 COG report by DuBois et al. showed that the choice of local control, between surgery and radiation, did not have a significant impact on OS.¹³ However, the risk of local failure was greater in those who received radiation rather than surgery, with a statistically significant hazard ratio of 2.41, although the anatomic sites treated with surgery (i.e., extremity, rib) are generally different from those treated with radiation (i.e., spine, sacrum, pelvis); so, these patient cohorts are often quite different. Nevertheless, radiation does have additional long-term effects, such as the risk of secondary malignancies.⁵ Surgical advances have continued to improve to allow for about 90% of extremity surgeries to be limb sparing, avoiding amputation as much as possible. Postoperative radiation is typically employed only if surgical margins are positive. For those patients receiving radiation as local control, it should be administered concurrently with consolidation therapy, specifically with the ifosfamide/etoposide portion. In addition, doxorubicin is held while radiation is being administered.⁷ If clinicians are treating according to the COG trial regimen, the week 13 doxorubicin dose is given just prior to the initiation of radiation and then followed by back-to-back cycles of ifosfamide/etoposide to avoid enhancement of normal tissue radiation toxicity expected with concurrent doxorubicin (Adriamycin).

The total radiation fractions and dose (measured in Gy) depend on the location of the primary site, on whether there was a resection with positive margins, or if there was metastatic disease. For example, the total recommended dose for gross disease is 55.8 Gy. However, if resected with microscopic residual (unable to obtain clean margins), then 50.4 Gy is used. In addition, for nonosseous lesions with complete response to chemotherapy, 50.4 Gy is used as well. Dose-escalated RT to limited fields may be beneficial for high-risk tumors and may reduce local recurrence rates. A single-institutional Phase 2 trial employed focal limited-margin RT using conformal or intensity-modulated techniques.⁸ Unresected tumors <8 cm at diagnosis received a standard dose of 55.8 Gy, and tumors >8 cm received an escalated dose of 64.8 Gy. Radiation is typically administered at a maximum of 1.5 to 1.8 Gy per fraction, given over an estimated 25 to 30 fractions. Given the variability in doses and fractions, the young age of the patients, and the need to integrate radiation with chemotherapy and possibly surgery, it is important to have a radiation oncologist well versed in treating EWS.

If a patient has metastatic disease at the time of diagnosis, the same systemic chemotherapy regimen is used. However, it is important to note that the five-drug regimen of VDC/IE was never shown to be more beneficial than VDC alone in treating metastatic disease. Also, the clinical trial demonstrating the superiority of administering chemotherapy every 2 versus 3 weeks did not include patients with metastatic disease; hence, the benefit of giving chemotherapy every 2 weeks has not yet been proved for metastatic disease. However, most oncologists will treat patients with metastatic disease with the same regimen used for localized disease, as most are reluctant to treat metastatic disease less aggressively than localized. The additional variability lies in local control, not only of the primary site but also of the sites of metastatic disease. It is dependent on where the metastatic disease is and if it can be surgically removed. Local control with radiation is also involved and the dose depends on the location site. For additional details of radiation in metastatic disease, refer to Chapter 4, Radiation Oncology.

METASTATIC DISEASE

About 25% to 30% of patients present with metastatic disease at the time of diagnosis. The incidence of metastatic disease at diagnosis correlates to the location of the primary tumor. Those with a central primary tumor, such as the pelvis, have the highest incidence of metastases at about 40%. Those with a proximal primary site have a 30% incidence of metastases. Also, those with a distal primary tumor have the lowest rate of incidence at about 15%.¹

EWS metastasizes most commonly to three specific locations: lung, bone, and bone marrow. Their incidence is about 38%, 31%, and <10%, respectively.¹ Metastatic disease can also appear in the brain, liver, and soft tissue; however, these sites are much rarer. Given the high rate of metastatic disease at diagnosis, it is imperative to get a chest CT and an FDG PET/CT for all patients at the time of initial diagnosis and staging. Chest CT is needed in addition to PET/CT as the PET is not of high-enough resolution to properly evaluate for pulmonary metastasis. Historically, bilateral bone marrow biopsies were done routinely at the time of diagnosis. However, the yield of bone marrow biopsy is extremely low and it is no longer performed by many practitioners unless required for clinical trials.⁵ Metastases to the bone marrow are not homogeneous, and therefore require a bilateral biopsy. Given

the lack of homogeneity of metastatic disease to the bone marrow, sampling error resulting in false negative can be a problem. In addition, if the FDG PET/CT is negative, the likelihood for finding metastatic disease in the bone marrow is extremely low. In general, bone marrow involvement can often be seen on PET/CT, thus calling into question the value of a bone marrow biopsy. Once a positive PET/CT is obtained and it is determined to be metastatic disease, a bone marrow biopsy will not impact the treatment plan. For these reasons, the bone marrow biopsy is falling out of favor as a diagnostic requirement.

Therapeutic Approach for Metastatic Disease

Despite advances in survival for localized EWS, metastatic disease in EWS continues to have an unacceptably poor prognosis outcome with <30% survival.⁵ Survival differs if metastases are limited to the lung only or have spread to the bone or bone marrow. When limited to lung metastases, the 5-year survival rate is slightly better than 30%, while if the disease has spread to other sites, survival rate is only 15% to 30%. Given this continued poor survival, treatment for metastatic disease should be encouraged to be given on clinical trials. At this time, the standard of care for metastatic disease at diagnosis consists of the same systemic regimen of interval-compressed VDC/IE used in North America, with other reasonable regimens being VDC, VAI, and VIDE. There are more options for metastatic disease because interval-compressed VDC/IE has not been shown to improve survival in metastatic disease. However, the standard of care remains the same, as most physicians do not feel comfortable treating metastatic disease less aggressively than localized disease. However, more aggressive systemic therapy with myeloablative chemotherapy with an autologous stem cell rescue has not been demonstrated as advantageous when given as induction therapy. Nevertheless, at relapse, some studies have demonstrated increased survival in chemotherapy-sensitive disease with an autologous stem cell rescue after high-dose chemotherapy, with the 5-year survival rate approaching 40% to 50%.⁹ Given the poor outcome to standard chemotherapy, one should encourage patients to enroll in clinical trials when available, which offer the potential for improved outcomes.

The current COG Phase 3 clinical trial for metastatic EWS is AEWS1221. This trial explores the addition of ganitumab to the current standard of care of VDC/IE. Ganitumab is a monoclonal antibody directed against IGF1R. It prevents the binding of the natural ligand IGF-1, and therefore prevents activation of the signaling pathway PI3K/AKT. Inhibition of this survival signal is thought to inhibit tumor cell proliferation and cause an induction of tumor cell apoptosis. This is an excellent front-line therapeutic option for metastatic disease. Additionally, this COG trial looks at the effectiveness of compressed intervals (from 3 to 2 weeks) in metastatic disease, as it has been shown to be effective in localized disease but not previously tested in metastatic disease. For those patients with pulmonary metastases, it is recommended to administer whole lung radiation (at a dose of 12–15 Gy) after the completion of systemic therapy.

Relapse disease typically occurs within the first 2 years after the initial diagnosis, most often in either the lungs or the bones. Three factors that give patients the highest risk for relapsed disease are metastatic disease at the time of diagnosis, a primary lesion in the pelvis, or a poor histologic response to neoadjuvant chemotherapy.⁵ Recurrent EWS has an estimated 5-year OS rate of <15%. However, those who have local-relapsed disease or later relapsed disease do still have a potential for cure. Researchers Rodriguez-Galindo et al. at St. Jude Children's Research Hospital reviewed their data of relapsed EWS patients. The 5-year relapse-free survival rate was 18%. However, those who relapsed >2 years from diagnosis had a 5-year relapse-free survival rate of 35%. In addition, those with isolated local relapse only had a slightly higher 5-year relapse-free survival rate of 22% versus the general 18%.¹⁴

In relapsed disease, enrollment into a clinical trial should also be strongly considered. However, if trials are not available, the patient does not qualify, or the patient declines, a few different therapeutic regimens exist.⁵ The two more commonly used regimens that give about 25% response rate are cyclophosphamide with topotecan and temozolomide with irinotecan plus vincristine. Another two options that have been used, with a lower response rate, are high-dose ifosfamide or gemcitabine plus docetaxel. The consensus opinion among experts in the field is to use the combination of temozolomide with irinotecan as the first option.⁵ It is intriguing that if an irinotecan-containing regimen fails, a patient would still be able to use a topotecan-containing regimen; despite being in the same family of drugs, they have different patterns of resistance. It is important to note that the response rates to the cyclophosphamide/topotecan regimen were correlated with the relapse interval. Those

who had disease progression while receiving therapy did not respond to this regimen. However, if >2 years had passed since the completion of therapy, then there was about a 50% response rate to this regimen.⁵

Cure is difficult to achieve in those patients with relapsed disease; patients who do receive therapy typically have a temporary response, with the median postrecurrence survival ranging from 9 to 17 months.⁵ From a quality of life perspective, it is important to note that those with painful lesions will typically respond to palliative radiation. There is insufficient data to support the use of high-dose chemotherapy with autologous stem cell rescue in these patients with relapsed disease at this time. A recent review by Tenneti et al.⁹ looked at the role of high-dose chemotherapy and autologous hematopoietic stem cell rescue (HSCT). It appears that giving high-dose chemotherapy followed by autologous HSCT after consolidation chemotherapy improved survival for some patients with EWS. In most of these studies, those who had high-dose chemotherapy followed by HSCT had an OS rate of 20% to 60% at 1 to 2 years and those who received consolidation chemotherapy had an OS rate of 20% to 25% at 5 years. The EFS rate for those with relapsed disease was 25% at 1 to 2 years for those with consolidation chemotherapy alone compared to 42% to 47% in those who had HSCT.⁹ Those that received high-dose chemotherapy followed by HSCT in induction did not demonstrate a survival benefit. However, the heterogeneity of the studies reviewed was so significant that no conclusive statement could be made. A prospective randomized controlled study is needed for these patients.

FOLLOW-UP

Once a patient has completed therapy and is in remission, there is a consensus that surveillance follow-up should be conducted for every patient. Surveillance consists of primary site imaging, lung imaging, and lab tests at various intervals: the first year it should be every 3 months, the second year every 3 to 4 months, the third year every 4 to 6 months, and then yearly during the fourth and fifth years after treatment. The primary site should have an x-ray exam and/or MRI with contrast. The MRI is necessary for those with a soft tissue primary lesion, as it will not be seen on x-ray. The lung surveillance consists of a non-contrast CT in the first and second years, followed by x-ray studies. Some patients will need follow-up nuclear medicine imaging, depending on if the PET/CT or bone scan at diagnosis was positive. However, if at diagnosis the nuclear medicine scan was negative, then no follow-up scans are needed. Given the cumulative dose of anthracyclines given during EWS treatment, an echocardiogram is recommended every 1 to 2 years, as is a complete blood count with differential.

SUMMARY

Though EWS is the second most common primary bone malignancy of childhood and young adulthood, it is a rare tumor. While most oncology practices will likely encounter some patients with EWS, only high-volume sarcoma centers see enough patients to truly develop expertise with this family of tumors. While the chemotherapy used is familiar to most oncologists, and general approach to treatment is relatively straightforward, the care of these patients is nuanced and can easily become exceedingly complex. At the very minimum, consultation with a high-volume sarcoma center, including involvement of properly trained and experienced orthopedic, medical/pediatric, and radiation oncologists, along with radiologists and pathologists, is essential for assuring the best outcome for these patients. Additionally, support services, including physical therapy, psychosocial services, and fertility preservation experts, are extremely valuable. These tumors require a multidisciplinary team approach, with excellent communication between the various members of the care team. Metastatic disease, the potentially significant side effects of the treatment regimens, and/or relapsed disease raise the complexity of the care of these patients exponentially and underscore the importance of expert involvement.

Biologically, EWS is one of the genetically “quietest malignancies,” driven by the defining translocation of *EWSR1-FLI1*. Despite this, much work is still needed to understand the underpinnings and heterogeneity within this family of tumors. Innovative treatments are currently being tested in clinical trials, with more to come. Sarcoma centers are propelling these advances in research and therapy, and should coordinate and collaborate with other centers and community practitioners to optimize the care for patients affected by this challenging malignancy.

CASE STUDY

Among the magnitude of cases that could be used to illustrate the complexity of EWS, this case was selected to demonstrate the importance of seeking treatment from teams with extensive experience in treating sarcomas, such as those that can be found at the sarcoma centers. This patient was a 20-year-old woman who initially presented with right-sided chest pain. The pain continued to worsen to the point that she sought medical care. Of note, at this time, the patient lived with her family outside the United States. The primary team initially did an ultrasound exam and chest radiograph to assess the area, and a bone mass was revealed arising from the right tenth rib. The patient was then referred to a surgical team. The surgical team attempted a complete resection of the mass and the right tenth rib at the time of diagnosis. The pathology returned as EWS, as fluorescence in situ hybridization (FISH) was positive for *EWSR1-FLI1* translocation. Unfortunately, for the patient, the correct surgical approach was not taken. In EWS of the chest wall/ribs, the standard approach is to remove the ribs above and below the lesion. Additionally, upfront surgery is not recommended for EWS, and instead, local therapy is typically to be done only after 12 weeks of chemotherapy. This approach increases the likelihood of negative margins, thus decreasing the risk for relapse. In contrast, this patient's surgery was done in her country of origin prior to any neoadjuvant chemotherapy. The patient then presented to pediatric oncology about 2 months after surgery. A repeat comprehensive staging workup was completed, including imaging of the primary site, chest CT, and a PET/CT. At this time, she was found to have metastatic disease with pulmonary nodules on the chest CT, which were not present initially at the time of her diagnosis. There were about six small pulmonary nodules of 2 to 3 mm in different areas of the left lower lobe of lung. In addition, the PET/CT was positive at the site of the initial lesion. Postsurgical changes could be seen; but given the time since surgery (about 2 months), the PET/CT was concerning for active disease. She was offered clinical trials, but did not enroll. She was then treated with interval-compressed VDC/IE. After 12 weeks of therapy, radiation was used for local control. She received right flank radiation at a dose of 50.4 Gy in 28 fractions. She then continued with consolidation therapy for 16 additional weeks. At the conclusion of her systemic therapy, she received whole lung radiation of 15 Gy in 10 fractions. Fourteen months after completion of therapy, she remains disease free, though still at high risk for recurrence. This case demonstrates two very important components of optimal care for EWS patients: the multidisciplinary approach with each team member (surgeon, medical/pediatric oncologist, radiation oncologist, pathologist, diagnostic radiologist) having a full understanding of the disease and how it is best treated and the need for comprehensive staging workup at diagnosis and relapse. Adherence to the recommended treatment guidelines could have altered the patient's outcome. To date, the patient remains disease free, but concern remains that the inappropriate surgical approach upfront has negatively impacted her prognosis. Another important feature of this case is that patients with EWS should be seen without delay by an experienced multidisciplinary team because of the risk of developing metastatic spread if systemic therapy is delayed. In this case, the patient may have been spared the addition of RT to both the chest wall and lungs, which places the patient at risk for future lung fibrosis and other secondary complications.

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