clinical recommendations
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Ewing's sarcoma of the bone: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Ewing sarcoma (ES)/primitive neuroectodermal tumor (PNET) of bone is the second most common primary malignant bone cancer in children and adolescents, but is also seen in adults, particularly the extraskeletal variety. The median age at diagnosis is 15 years and there is a male predilection of 1.5/1. ES is diagnosed in white Caucasians at an incidence of 0.3/100 000 per year, but is very uncommon in the African and Asian population.

diagnosis

The first symptom of bone ES is usually pain—often erroneously attributed to trauma. Plain radiographs in two planes, complemented by computed tomography (CT) and/or magnetic resonance imaging (MRI) are indicative of a malignant tumor. Before biopsy patients with suggestive findings should be sent to a reference centre with particular experience in the disease. The definitive diagnosis is made by biopsy, providing sufficient material for conventional histology, immunohistochemistry and molecular biology (fresh, unfixed material). ES is a small blue round-cell tumor, PAS- and CD99 (MIC2)-positive. All ES are high-grade tumors. While the degree of neuronal differentiation used to be applied to distinguish between classical ES and PNET, molecular biology studies have now shown that all these tumors share a common gene rearrangement involving the EWS gene on chromosome 22, so that this distinction is now obsolete. In most cases, a reciprocal translocation t(11;22)(q24;q12) is found, but t(21;22)(q22;q12) and others may also occur [t(7;22), t(17;22) and t(2;22) translocations and inv(22)].

staging and risk assessment

Before biopsy, the description of the local extent of a bone tumor requires radiographic and CT/MRI of the entire involved bone, including adjacent joints and soft tissues. For planning of local therapy, the precise involvement of bone, bone marrow and soft tissues including the relationship to critical structures like nerves or vessels, must be specified. A chest CT scan is required to rule out lung or pleural metastases. The assessment for bone and bone marrow metastases is to include 99mTc bone scintigraphy, to detect osseous metastases, and light microscopical examination of bone marrow aspirates and biopsies taken at sites distant from the primary tumor. Positron emission tomography (PET) scanning for bone metastases and PCR techniques to investigate for bone marrow metastases are sensitive methods currently under evaluation. Additional appropriate imaging studies and biopsies should be taken from suspicious sites, as the exact staging of the disease has an impact on treatment and outcome [III, B].

About 20% of patients have ES of the pelvic bones, while 50% show extremity tumors. ES may involve any bone and (less commonly in non-adult patients) soft tissues. Between 20% and 25% of the patients are diagnosed with metastatic disease (10% lung, 10% bones/bone marrow, 5% combinations or others).

With surgery or radiotherapy alone, 5-year survival is <10%. With treatment in current multimodality trials including chemotherapy, survival is ~60–70% in localized and ~20–40% in metastatic disease. Bone metastases confer a poorer outcome than lung/pleura metastases (<20% compared with 20–40% 5-year survival) [IIa, B]. Other known prognostic factors are tumor size or volume, serum lactate dehydrogenase (LDH) levels, axial localization or older age (>15 years). Under treatment, poor histological response to preoperative chemotherapy, and incomplete or no surgery for local therapy are further adverse prognostic factors [IIa, B].

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treatment plan

As ES is a rare cancer, and its management is complex, the accepted standard is treatment in reference centres or within reference networks.

localized disease

Multimodal approaches within clinical trials, employing combination chemotherapy and surgery and/or radiotherapy, have raised 5-year survival rates from <10% to >60%. All current trials employ three to six cycles of initial chemotherapy after biopsy, followed by local therapy and another six to ten cycles of chemotherapy usually applied at 3-week intervals. Treatment duration is thus 8–12 months. Agents considered most active include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin and etoposide. Virtually all active protocols are based on four- to six-drug combinations of these substances. Protocols that have proved to be most effective include at least one alkylating agent (ifosfamide or cyclophosphamide) and doxorubicin [Ib, A].

Despite lively debate, complete surgery, where feasible, is regarded as the best modality of local control. Radiotherapy should be applied if complete surgery is impossible, and should be discussed where histological response in the surgical specimen was poor (i.e. >10% viable tumor cells) [IV, C]. In one large series it was found that incomplete surgery followed by radiotherapy was not superior to radiotherapy alone. Radiotherapy is applied at doses of 40–45 Gy for microscopic residues and 50–60 Gy for macroscopic disease [III, B].

Treatment of patients with extraskeletal ES follows the same principles as for bone ES. Criteria for pathologic tumor response assessment are less established. Radiation therapy is used more extensively after surgery.

Treatment of adult patients follows the same principles. However, tolerability of therapies in adults needs to be taken into account when transferring treatment protocols conceived for children and patients of age ≤30–40 years.

metastatic and recurrent disease

Outside specific clinical trials, patients with metastatic disease ought to receive similar therapy to that given for localized disease, with appropriate local treatment of metastases, commonly applied as radiotherapy. Several non-randomized trials have assessed the value of more intensive, time-compressed or high-dose chemotherapy approaches, followed by autologous stem cell rescue, but evidence of benefit, e.g. resulting from randomized trials, is lacking [III, B]. In patients with lung metastases, the resection of residual metastases after chemotherapy, and possibly whole lung irradiation, may confer a survival advantage [III, B]. Patients with bone or bone marrow metastases and patients with recurrent disease still fare poorly, with 5-year survival rates of ≤20%.

The only prognostic factor identified in relapse seems to be time to relapse: patients relapsing later than 2 years from initial diagnosis have a better outcome [III, B]. Doxorubicin therapy is usually no longer feasible due to previously achieved cumulative doses. Chemotherapy regimens in relapse situations are not standardized and are commonly based on alkylating agents (cyclophosphamide, ifosfamide) in combination with topoisomerase inhibitors (etoposide, topotecan) or irinotecan with temozolomide [III, B].

follow-up

Most relapses occur in the first 3 years of follow-up; late relapses have rarely been observed even after 15 years or longer. Besides the detection of relapse, long-term sequelae of treatment are the main concern in long-term follow-up. Impaired renal function may be observed early in follow-up, but cardiac or pulmonary damage may become apparent later. Secondary cancers may arise in irradiated sites. Secondary leukemia, particularly acute myeloid leukemia may rarely be observed independent of previous irradiation as early as 2–5 years after treatment [III, B]. Follow-up intervals should be 2–3 months during the first 3 years, 6 months until 5 years and at least once yearly thereafter.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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