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Anti-Tumour Treatment

Osteosarcoma treatment – Where do we stand? A state of the art review

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ABSTRACT

Long-term outcome for patients with high-grade osteosarcoma has improved with the addition of systemic chemotherapy, but subsequent progress has been less marked. Modern, multiagent, dose-intensive chemotherapy in conjunction with surgery achieves a 5-year event-free survival of 60–70% in extremity localized, non-metastatic disease. A major, as yet unsolved, problem is the poor prognosis for metastatic relapse or recurrence, and for patients with axial disease. This article reviews the current state of the art of systemic osteosarcoma therapy by focusing on the experiences of cooperative osteosarcoma groups. Also, we shed light on questions and challenges posed by the aggressiveness of the tumor, and we consider potential future directions that may be critical to progress in the prognosis of high-grade osteosarcoma.

Introduction

Following the implementation of chemotherapy in the 1970s, the treatment of high-grade malignant osteosarcoma (OS) has made important progress. However, survival rates continue to be unsatisfactory in the metastatic and relapse setting. Understanding OS biology still remains a complex challenge. An unknown etiology, high genetic instability of OS cells, a wide histological heterogeneity, lack of biomarkers, high local aggressiveness, and a rapid metastasizing potential create pivotal questions to be answered. The purpose of this paper is to outline recent developments in the field of osteosarcoma therapies.

Search strategy and selection criteria

We searched PubMed for the past 12 years (January 2001–October 2013) with the terms "osteosarcoma" and "treatment". The abstracts were screened to identify those research studies and review articles we judged relevant to our objectives. This procedure identified 166 potentially eligible publications which were studied in detail. A particular relevance was given to reports on systemic therapy. References from these articles were also obtained, and review articles are cited to provide readers with more details than this review has room for. The date of the last search was October 8, 2013.

What do we know about OS?

Background

Osteosarcoma (OS) defines neoplasms that share the histological finding of osteoid production in association with malignant mesenchymal cells. These tumors are generally locally aggressive and tend to produce early systemic metastases [1]. A distinction is generally drawn between different histologic types of OS (conventional, teleangiectatic, parosteal, periosteal, low-grade central, small cell, not otherwise specified). The conventional type is

Abbreviations: OS, osteosarcoma; SEER, Surveillance Epidemiology and End-Results Program of the US National Cancer Institute; MSKCC, Memorial Sloan-Kettering Cancer Center; COG, Children's Oncology Group; OAS, overall survival; EFS, event-free survival; HDMTX, high-dose methotrexate; (SSG), Scandinavian Sarcoma Group; EURAMOS-1, European and American Osteosarcoma Study Group 1 trial; MAP, high-dose methotrexate and doxorubicin and cisplatin; COSS, Cooperative Osteosarcoma Study Group; EOI, European Osteosarcoma Intergroup; SMNs, second malignant neoplasms; HER2/neu, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; MTP-PE, muramyl tripeptide phosphatidylethanolamine = mifamurtide; G-CSF, granulocyte-colony stimulating factor; IOR, Istituto Ortopedico Rizzoli; IFN-α, interferon alpha; POG, Pediatric Oncology Group; ISG, Italian Sarcoma Group; SFOP, Société Française D'oncologie Pédiatrique.

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the most common, and has been subdivided based on the predominant features of the cells (osteoblastic, chondroblastic, fibroblastic), although without clear significant differences of clinical outcome [2]. This article addresses high-grade osteosarcoma, which accounts for 80–90% of all OS [3]. In the majority of primary OS, the etiology is unknown. Cytogenetic studies have shown various complex changes involving some chromosomes but without any specific pattern [4]. Two genes – a hereditary mutation of retinoblastoma, and an autosomic recessive mutation of p53 in the Li-Fraumeni syndrome – localized in 13q14 and 17p13, respectively, are currently proposed to be involved in a stepwise accumulation of genomic defects [4].

Epidemiology

OS is classified as an orphan disease with an overall incidence of 0.2–3/100 000 per year (0.8–11/100,000 per year in the age group 15–19 years) in the EU [3]. Despite its rarity, it has been reported to be the third most common cancer in adolescence, occurring less frequently than only lymphomas and brain tumours in this age group [5]. An association between rapid bone growth and osteosarcoma has been postulated, given the tumor's typical metaphyseal location and its peak incidence during adolescence and early adulthood as well as the male predominance of 60% [6]. OS is extremely rare in children before the age of 5 years [7].

Tumor sites

The most common primary sites of OS are the distal femur, the proximal tibia, and the proximal humerus, with more than half originating around the knee [8,9]. About 10% develop in the axial skeleton, most commonly the pelvis [10,11]. An analysis of the SEER database revealed a higher percentage of axial tumors in patients aged 60 and above (39.7%) when compared to patients aged $\leqslant$25 (12.2%) or 25–59 years (35.3%) [12]. It is well established that axial locations result in a considerably worse outcome than primary disease location within the appendicular skeleton [10,12]. The 5 year survival of OS in the pelvis ranges from 27% to 47% [13]. OS in the spine has been linked with median survival times of 10–38 months [14,15]. A recently published report from the Children's Oncology Group (COG) found that survival with metastatic disease in the absence of a pelvic primary tumor was similar to that for localized or metastatic pelvic OS [16].

Metastatic disease and local recurrence

At the time of OS diagnosis, about 10–20% of patients present with macroscopic evidence of metastatic disease, most commonly (90%) in the lungs, but metastases can also develop in bone (8–10%) and rarely in lymph nodes [8,17–19]. However, 80–90% of patients are assumed to have micrometastatic disease, which is subclinical or undetectable using current diagnostic modalities [6]. Regarding lung metastases, thoracic CT-scanning is considered gold standard and remains the most reliable imaging tool [20]. In OS patients with radiographic pulmonary metastases, CT, however, has two limits: not all lung nodules found during surgery are evident on the CT scan, and not all nodules seen on the CT scan are true metastatic lesions, in particular in lesions smaller than 5 mm [21].

A total of 30–40% of patients with localized OS will develop a local or distant recurrence [22]. Approximately 90% of relapses are lung metastases, which usually occur in the first 2–3 years [14,23–25]. Relapse 5 years after initial treatment of OS is uncommon, arising in between 1% and 2% of all osteosarcoma patients [26]. Hauben et al. found a trend for late relapse to arise more commonly in chondroblastic subtypes [26]. Osteosarcoma recurrences are associated with a rather poor prognosis [22,27]. Five-year overall survival (OAS) for recurrent OS has been reported to be 23–29% (pulmonary metastases only: 28–33%) [20]. In one series of patients who relapsed, 31% of those with local recurrence alone were cured by further treatment, as compared with only 10% of those with metastases [28]. The outlook is considered to be extremely poor for patients who present with synchronous regional bone metastases (skip metastases), either in the primary bone site or transarticular [29]. Aggressive multimodal therapy holds the promise to achieve prolonged survival, especially in patients in whom these metastases occur within the same bone as the primary lesion and whose tumors respond well to chemotherapy [30]. Bielack et al. reported survival estimates with second and subsequent osteosarcoma recurrences. Five-year OAS and event-free survival (EFS) rates were 16% and 9% for second, 14% and 0% for third, 13% and 6% for fourth, and 18% and 0% for fifth recurrences, respectively [31]. The median interval from first to second recurrence was found to be nine months, and the median interval between subsequent recurrences remained quite constant at approximately 6 months [31].

Current therapeutic strategies

Current management comprises preoperative (neoadjuvant) chemotherapy followed by surgical removal of all detectable disease (including metastases), and postoperative (adjuvant) chemotherapy, preferably within the setting of clinical trials [17]. OS is considered resistant to applicable doses of radiation [23,32]. Supplemental therapeutic approaches such as chemoembolization or angio-embolization, thermal ablation, radiofrequency ablation, and cryotherapy are experimental [23].

Surgery

Complete surgical resection, if feasible, remains essential for cure [23]. Current surgical strategies focus on refining the nature and scope of resection to preserve uninvolved tissues, and on the adoption of novel biological and nonbiological skeletal and soft-tissue reconstruction methods to optimize function [33]. Advances in imaging techniques and positive effects of preoperative chemotherapy have led to a major shift away from amputation towards limb-salvage (conservative) surgery, with the latter being expanded to around 80% of patients [9,34]. Local recurrence rates of 2–3% after amputation and 5–7% after conservative surgery have been reported, with no significant differences in survival [23,35]. The incidence of local recurrence has been closely related to the achieved surgical margins (intralesional – within lesion, marginal – within reactive zone, wide – through normal tissue and beyond reactive zone, radical – extracompartmental), with only a wide margin being considered appropriate [23,28]. Even so, no general definition exists on the adequate thickness of the normal cuff, also as this varies depending on layers of reactive tissue surrounding the tumor and the responsiveness to preoperative chemotherapy. In OS patients who achieved complete surgical remission with adequate margins, surgical margin width in bone did not correlate with the local recurrence rate [36].

Thoracotomy with metastasectomy remains an essential and effective adjunct to multiagent chemotherapy in the treatment of pulmonary metastases. Surgical resection is considered if all lung nodules can be removed and a sufficient amount of pulmonary tissue can be saved to maintain adequate pulmonary function [23].

Chemotherapy

Recently, most chemotherapy regimens applied for OS have been based around 4 drugs; high-dose methotrexate (HDMTX)