EDITORIAL COMMENT

Osteosarcoma: Is Age an Issue?

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Osteosarcoma (OS) is the most commonly diagnosed primary malignancy of bone, particularly among children and adolescents.[1] During the last 25 years, remarkable progress has been made in the treatment of OS. The combination of chemotherapy and limb-sparing surgery for OS patients has led to an overall 5-year survival rate of around 70% and limb preservation rate of >90% for localized disease.[2] However, 30–50% of patients with initially localized disease subsequently developed recurrence, and 20–30% of newly diagnosed cases presented with metastatic disease. In cases of recurrent or metastatic tumor where complete resection is not possible, the 3-year progression-free survival is 0% due to failure of rescue chemotherapy.[3] It is therefore crucial to identify the prognostic factors in patients with OS to predict treatment response, recurrence and survival.

Several prognostic factors have been identified by previous studies, including age, tumor size, histological type, and site. However, reporting of such associations across different studies has often been inconsistent. Recently, there was an international collaboration of 10 teams of investigators (including 2,680 patients), and the prognostic significance of traditional clinical predictors in OS was evaluated. In multivariate models, patients with poor histologic response to chemotherapy, having metastatic disease at diagnosis, or on chemotherapy regimens not including anthracycline, had higher chance of death, distant metastasis and local recurrence. Amputation instead of limb salvage/wide resection was predictive of a higher risk of mortality and distant metastasis. Development of local recurrence when the patient was first seen was an independent prognostic factor associated with death and local recurrence. In this study, the prognostic influence of age at the start of the follow-up period was also investigated. Older age was associated with poor survival (7% relative risk increase per decade) and increased risk of local recurrence.[4] This is consistent with previous reports. One possible explanation is that there is a high percentage of OS with Paget's disease and OS as a second or later cancer among the elderly. These so-called secondary OS are considered chemoresistant and are more difficult to treat.[1]

However, this study did not address the issue of whether or not patients of younger age (<10 years old) may have worse outcome. In this issue of the *Journal of the Chinese Medical Association*, Hsieh et al report a paper discussing the prognostic influence of younger age on OS.[5] As the authors mention in their paper, currently available studies have conflicting results. Kim et al developed a prognostic nomogram for predicting the 5-year probability of developing metastasis after neoadjuvant chemotherapy and definitive surgery based on 365 OS patients treated at a single institution.[6] Multivariate Cox model disclosed that patient age at diagnosis, tumor size, humeral location, and tumor necrosis rate after chemotherapy were correlated with metastasis-free survival. In the analysis of age, they found a poor outcome in both older patients (age> 40 years) and a subgroup of patients aged 12–15 years, which represents the period of undergoing growth spurt. Patients aged <12 years actually did better than these 2 groups.[6] This is consistent with previous studies. It seems that the prognostic influence of age may reflect the underlying biology of cancer development (growth spurt).

If that is the case, we can look at this issue from a tumor biology viewpoint. Several genetic mechanisms have been associated with OS tumorigenesis. These include cell genomic changes associated with cycle alterations, such as *TP53*, *RB1*, and *MDM2*, disturbance of cell senescence pathways resulting from telomere dysfunction, and alterations in cell death/cytokine pathways resulting from *FAS* dysregulation.[7] Retinoblastoma survivors have an increased incidence of second malignancies, the majority of which are OS.[8] Loss of heterozygosity of *RB1* has been associated with

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poor event-free survival in OS patients,[9] and was associated with a significantly younger age at diagnosis.[8] However, most of these studies have limited case number, and further confirmation in larger scale surveys is warranted.

Hsieh et al found that patients aged ≤ 10 years had a higher chance of poor response to chemotherapy.[5] The classic example of chemoresistance is multidrug resistance (MDR) mediated by the *MDR1* gene. The protein product of *MDR1*, P-glycoprotein (Pgp), is a plasma membrane protein that acts as an adenosine triphosphate-dependent efflux pump responsible for removing cytotoxic molecules, including chemotherapeutic agents, from cells. High levels of *MDR1* gene expression has been considered to be a prime mechanism of drug resistance in OS. However, in a meta-analysis of 14 studies (including 631 patients) that evaluated the correlation between Pgp and histologic response to chemotherapy and clinical disease progression (death, metastasis or recurrence), Pgp was not found to have discriminating ability to identify poor responders versus good responders to chemotherapy, but instead had strong associations with the risk of disease progression.[10] So the expression of Pgp may be considered a prognostic factor. Serra et al found that patients younger than 12 years had a higher chance of relapse and shorter event-free survival, and there was a clear trend toward a higher frequency of Pgp expression in this group of patients.[11] So overexpression of Pgp may explain the relatively poor outcome in some of the younger OS patients.

Other factors may influence the outcome in younger patients, such as delayed diagnosis due to unawareness of the symptoms, and higher chance of chemotherapy-induced toxicity leading to intolerance to treatment.[12] However, these factors need further clarification. In summary, age is considered a prognostic factor in OS. Older age (> 40 years) is associated with poor survival and increased risk of recurrence, possibly attributed to the relatively chemoresistant nature of secondary cancer. However, the prognostic significance of younger age (< 10 years or preadolescent) remains controversial. An international collaborative study is necessary to answer the following questions: (1) Do patients younger than 10 years actually do worse than older patients? (2) If the answer to question 1 is affirmative, are there any biomarkers that are associated with this poor outcome? (3) If such markers can be identified, could these markers be used as diagnostic or therapeutic targets? Through this joint effort, hopefully we can further improve the care of OS patients.

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