Chemotherapy

Does Neoadjuvant or Adjuvant Therapy Improve Outcomes?

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KEYWORDS

• Soft tissue sarcoma • Surgery • Chemotherapy • Multimodality therapy
• Limb salvage • Survival

KEY POINTS

- More effective systemic therapy is a critical unmet need in the combined modality therapy of locally advanced soft tissue sarcoma.
- Meta-analyses of adjuvant/neoadjuvant clinical trials of chemotherapy for soft tissue sarcoma show a modest, but statistically significant, improvement in oncologic outcome favoring chemotherapy.
- Adjuvant/neoadjuvant chemotherapy for soft tissue sarcoma has not been widely adopted in large part because of the modest benefits and substantial risk of toxicity from intensive anthracycline-based regimens.
- Outcomes with adjuvant/neoadjuvant chemotherapy in soft tissue sarcoma vary by histologic subtype, and approaches based on tumor histology and individual patient and tumor factors are indicated.

INTRODUCTION

Soft tissue sarcomas (STS) are an uncommon and diverse group of tumors with mesenchymal differentiation, accounting for approximately 1% of US cancer diagnoses annually.[1,2] As such, clinical behavior of these tumors can vary greatly, and robust prospectively obtained outcomes data are difficult to achieve. The rarity of incidence and diversity of disease biology also make consensus on treatment guidelines challenging, especially for key clinical questions in which the benefit/risk ratio for therapy may be narrow. As a general rule, the primary treatment modality for nonmetastatic STS in all locations and for most histologic types remains wide en bloc surgical resection, frequently in combination with radiotherapy (RT). Although distant disease control

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and effective systemic therapy remain critical unmet needs in the multimodality management of STS, the role of systemic therapy in the management of primary, nonmetastatic disease remains an area of significant debate.[2,3]

Overall, local therapy, particularly for extremity and body wall/truncal STS, has proven highly effective. For the past 30 years, function-preserving/limb-sparing surgery combined with RT has successfully replaced amputation and other radical extirpative procedures in 90% to 95% of patients with STS.[1–3] Long-term local control rates with these combined modality approaches exceed 85% to 90%. However, distant control and overall survival (OS) remain a challenge, particularly for patients with more aggressive disease (typically characterized by tumors larger than 10 cm, high-grade histology, and/or histologic subtypes with high risk of metastasis, such as synovial sarcoma, myxoid/round liposarcoma, and undifferentiated pleomorphic sarcoma).[4] In fact, patients with high-grade tumors (typically American Joint Committee on Cancer [AJCC] stage III) have a risk of distant recurrence and death as high as 50% within 5 years of diagnosis.[4,5] For these patients, neoadjuvant/adjuvant chemotherapy has frequently been advocated to improve metastasis-free survival and OS. However, the role of chemotherapy in the treatment of patients with STS amenable to complete surgical resection remains a controversial subject. The handful of prospective studies showing survival, local-recurrence, or distant-recurrence benefits to adjuvant/neoadjuvant chemotherapy in localized STS are mitigated by other studies demonstrating no benefit.[2]

In this article, we focus on the role of chemotherapy in the definitive management of STS amenable to surgical resection with curative intent. Although current data are equivocal and the approach to adjuvant/neoadjuvant chemotherapy varies by institution, by specialty, and even by practitioner, there is increasing recognition that outcomes with adjuvant/neoadjuvant chemotherapy in STS vary by histologic subtype and that multimodality treatment approaches based on tumor histology and individual patient and tumor factors are indicated.[5,6]

TREATMENT APPROACHES

Current National Comprehensive Cancer Network (NCCN) guidelines for the multimodality management of STS, particularly for locally advanced disease amenable to resection with curative intent, clearly endorse management by sarcoma specialists in a tertiary referral center.[2] However, the specific recommendations regarding treatment sequencing and specific modalities (such as chemotherapy and RT) used in a combined modality approach are equivocal. Wide, but function-preserving, surgery in combination with RT remain the backbone of therapy in all possible treatment scenarios in which curative treatment is the goal. Moreover, NCCN guidelines acknowledge that it is acceptable to either include or omit chemotherapy from combined modality treatment, even in cases of locally advanced/stage III disease (http://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf) despite the substantial risk of distant disease progression and death.

As a result, there is wide variation in the utilization of adjuvant/neoadjuvant chemotherapy in the management of primary STS. For example, an analysis by Wasif and colleagues[7] showed that orthopedic oncologists and physicians with more than 75% of their clinical practice devoted to patients with sarcoma had the greatest preference for chemotherapy in the adjuvant/neoadjuvant management of STS. In contrast, surgical oncologists reported a statistically significant lower predilection for incorporating chemotherapy into the treatment plan for patients with locally advanced STS. Overall, the results of this survey study reinforced the impression