Preoperative Chemotherapy for Stage IIIB Extremity Soft Tissue Sarcoma: Long-Term Results From a Single Institution

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Background
Soft tissue sarcomas (STS) are uncommon but not rare. They are tumors of mesenchymal origin which are usually localized at the time of diagnosis. Local control is thus very well preserved in most patients with surgical or radiation treatments, but 50% will die from distant metastases. Thus, a good systemic treatment is needed.

Doxorubicin (Adriamycin) - based chemotherapy has been the most effective to date against this malignancy. In the December 6th 1997 issue of the Lancet, a meta-analysis from the Sarcoma Meta-analysis Collaboration revealed results from their review of adjuvant chemotherapy trials from all over the world. This was performed due to the small number of cases in each study in an attempt to tease out some advantage to utilizing adjuvant chemotherapy. There was no significant overall survival advantage at 10 years, but a significant local relapse free survival (LRFS), distant metastases free survival (DMFS) and overall relapse free survival (ORFS) of 6%, 10% and 10%, respectively.

University of Texas M.D. Anderson Cancer Center reviewed their data on preoperative or neoadjuvant chemotherapy in these types of patients. This article details their results.

Materials and Methods
Data from retrospective review of patients with STS of the extremities treated preoperatively with Doxorubicin-based chemotherapy was reported. From 1986 to 1990, over 500 patients with STS were evaluated at the M.D. Anderson Cancer Center. A subset of 76 patients presented with AJCC stage IIIA (grade 3 or 4, T2/N0/M0) were treated with preoperative chemotherapy. All but one received doxorubicin-based chemotherapy with the vast majority getting doxorubicin, dacarbazine with or without cyclophosphamide. A median of 3 cycles of therapy was given prior to surgery and/or radiation. One third of the patients got further chemotherapy once the local therapy with surgery and/or radiation was finished.

Response to chemotherapy was documented with radiographic (CT or MRI?s) volume of the tumor. The designations were complete response (CR - no radiographic evidence of residual tumor), partial response (PR - greater than or equal to 50% reduction in tumor volume), minimal response (MR - 15 - 49% reduction in tumor volume), stable disease (SD - no more than 15% increase or decrease in tumor volume) and progressive disease (PD - greater than 15% increase in tumor volume).

Results
Limb sparing surgery was performed on 91%, while the other 9% had amputations. Fifty-eight percent of patients had radiation therapy (approximately half had post-chemotherapy/preoperative and the others had postoperative). The doses preoperatively were 5000 rads or centi-Gray and 6500 cGy postoperatively.

The radiographic CR, PR, MR, SD and PD rates were 9%, 19%, 13%, 30% and 30%, respectively. The patients who had radiographic CR (rCR) did not have pathological CR (pCR). Four patients (6%) had a pCR: three patients with rPR and one with rSD.

Median follow-up was 85 months (range 61 - 111). Median time to local recurrence was 11 months. Five-year LRFS was 83% with no significant difference in those that had an objective response (rCR and rPR) versus those that did not (rMR, rSD and rPD). Median time to distant recurrences was 11 months also. The five-year DMFS was 52% and also had no difference in objective responders versus non-responders. The ORFS at five-years was 46%. The absolute overall survival (OS) was 54% at 5 years while the actuarial figure was 59%. Again there was no difference in objective responders versus non-responders.
Discussion

Neoadjuvant chemotherapy seems to be a logical way to progress in this disease since the main mortality in this disease is from metastatic disease. Perhaps using systemic therapy up-front will decrease the likelihood of micrometastases spreading while one is pursuing local therapy with surgery and radiation therapy. The results of this retrospective review seem to champion the cause. The DMFS and OS in these high grade patients are comparable to studies where all grades of tumors are evaluated. As with all retrospective studies, it difficult to make clear conclusions on the benefit of preoperative chemotherapy as these patients are treated in variety of manners (postchemotherapy/preoperative or postoperative radiation therapy or postoperative chemotherapy). The chemotherapy was also not uniform. All we can truly confirm is that it appears to be possible option at approaching a malignancy that has its most problem at being controlled systemically.

There needs to be a phase III trial comparing neoadjuvant chemotherapy versus postoperative chemotherapy versus no adjuvant chemotherapy. The problem is in the implementation of such a trial since most patients are operated on before any radiation oncologist or hematologist oncologist has a chance to evaluate the patient. The paucity in the occurrence of STS is also a limiting factor in this trial. The EORTC to date has performed the largest single randomized trial on STS of many sites and grades of tumor comparing adjuvant postoperative chemotherapy versus no adjuvant chemotherapy. The patients who received adjuvant chemotherapy did significantly better in LRFS and overall disease free survival, but no different in DMFS or OS.

Thus, there appears to be a slight benefit to adjuvant therapy in disease control, but when to give therapy is perhaps the question that is yet to be answered.