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PERSPECTIVE

Preoperative chemotherapy for soft tissue sarcomas: reinventing the wheel

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Over 30 years ago we published the first experience using preoperative chemotherapy for osteosarcoma of bone [1]. It was initially conceived with Dr. Ralph Marcove to allow time to custom produce an endoprosthesis for the first limb salvage treatment for osteosarcoma (rather than the standard amputation). Although criticized by some surgeons claiming that we wouldn't even cure the 10% that were cured with immediate amputation, we continued with the hope that immediate shrinkage of the primary tumor with systemic therapy would not only allow limb salvage surgery, but would lead to fewer metastasizing tumors and a higher cure rate. We monitored the tumors with daily examinations, determination of the alkaline phosphatase (if elevated) and by 1979 the first positron emission tomography (PET) scans (that's right 29 years ago) done before and within weeks of starting therapy to ensure against failure [2]. Those first results reported in 1979 were so spectacular that many found them hard to believe. Not only were we able to perform limb salvage therapy, but the cure rate for that first cohort of 31 patients was (and still is) in excess of 80% [3]. With Dr. Andrew Huvos we designed a grading system for the histologic effect of preoperative chemotherapy on the resected primary tumor. To our surprise 100% of those that had a favorable histologic effect were disease-free survivors at the time of the data analysis [3]. A larger study published in 1982 confirmed these significant findings [4]. Following this publication numerous studies around the world confirmed the fact that the response to preoperative chemotherapy was the most important prognostic indicator for survival.

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Preoperative chemotherapy had many advantages:

1. It shrunk the tumor in the advancing infiltrating margin (the most malignant part of the tumor) making limb salvage surgery with truly negative margins more probable.
2. It became the impetus to do more limb salvage surgery with the hope of cure.
3. It allowed decisions about postoperative therapy to be more scientifically rational (depending upon the preoperative response).
4. It helped to define optimal doses [5] and types of chemotherapy that would make the tumor respond, thus defining the best postoperative chemotherapy.
5. Its effect was still the best predictor of disease-free survival, and became the standard for treating osteosarcoma.

It was this rational approach (dubbed "neoadjuvant chemotherapy") to cancer treatment that was adapted to many other cancers, including gastric, anal, rectal, esophageal, late stage breast, and even certain large lung cancers to name a few. However it was not yet accepted for osteosarcoma's closest cousin, the high grade malignant soft tissue sarcoma.

When I arrived in Los Angeles at UCLA I met Dr. Frederick Eilber, the subsequent chief of surgical oncology at UCLA. He was impressed by our osteosarcoma results and we decided to continue his early attempts to repeat this work with soft tissue tumors of high grade malignancy [6]. However it wasn't until 1990 when Ifosfamide became available in the United States, and the demonstrated efficacy of high doses 14–20 g/M^2 in classically recalcitrant tumors (e.g., synovial sarcoma) [7, 8] that we began treating all high grade soft tissue sarcomas with preoperative chemotherapy containing high dose ifosfamide (and cis-platinum and Adriamycin) and preoperative radiation therapy (Table 1). Our philosophy was that these tumors, if they were to be cured, needed to be cured by surgery locally. Without local control very few (if any) would be cured.

Table 1 >500 T-18 Pre-Op. (high dose Ifosfamide containing protocol) treated STS patients LR rate

Site	Local rec. rate
Extremity	6%
Head and neck	14%
Retroperitoneal	43%

Local recurrence rate in high grade soft tissue sarcoma patients treated with preoperative high dose ifosfamide containing chemotherapy and preoperative irradiation (no wound healing problems with R.T. delivered at standard equivalent doses of <45 Gy) These LR rates are about ½ of that seen without preoperative chemo-radio therapy)
LR Local recurrence; *STS* soft tissue sarcoma

It was much easier to obtain surgical control at the first attempt rather than after a local recurrence. Irradiation and chemotherapy given postoperatively might only delay a local recurrence, but if given preoperatively, it might make surgical cure more possible by sterilizing the rapidly infiltrating microscopically advancing margin of the tumor.

In addition preoperative (or "neoadjuvant") therapy, it was hoped, would also yield all of the prognostic information and postoperative treatment decision-making as it did in osteosarcoma. After treating several hundred soft tissue sarcoma patients, our analysis proved correct (Table 2).

In addition to dramatically lowering the recurrence rate, as in osteosarcoma the effect of preoperative therapy on the primary tumor turned out to be a powerful prognostic indicator [9, 10].

This work was done with surgery at UCLA with the surgeons Fredrick Eilber and Jeffery Eckardt. Subsequently Dr. Eilber's son, while a surgical oncology fellow at the Memorial Hospital in New York compared our UCLA-treated patients with the patients with similar high grade tumors treated without preoperative therapy in New York. Because of the large number of patients, we were able to look at homogeneous groups of patients with the same type of high grade soft tissue sarcoma. The positive effect of preoperative therapy in this contemporary (but nonrandomized) group was quite notable [11, 12] (see Fig. 1).

After the presentation of our original data in 1993 (and published in 1995) [6] it was mostly ignored by the rest of the American oncology community (similar to the history of osteosarcoma). But it is slowly working its way across

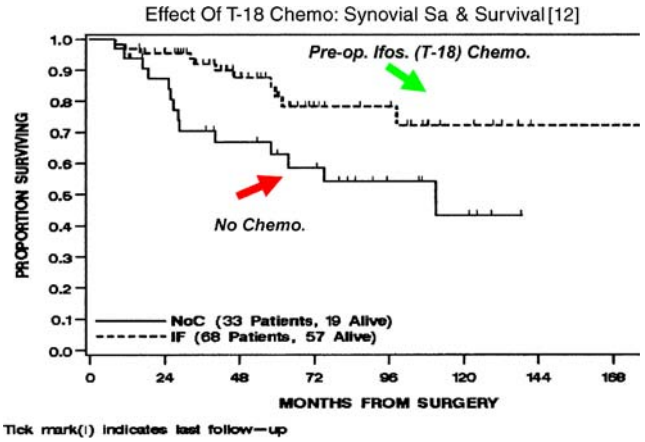

Fig. 1 Overall survival of patients with high grade synovial sarcoma: neoadjuvant therapy vs. no chemotherapy. All but three UCLA patients were given preoperative chemotherapy and radiation therapy (<45 Gy). The remainder of the "No Chemo" group was treated at the Memorial Sloan Kettering Cancer Center in New York. Reprinted with permission from Eilber et al. [6]

America, Scandinavia, and the European Continent almost 15 years later.

The rules for the successful deployment of this powerful treatment modality for high grade soft tissue sarcomas are as follows:

1. All abnormal lumps should be incisionally biopsied only. Should it prove to be benign, a good excision can then be done. Don't be fooled by "low grade myxoid" terms to describe tumors such as liposarcoma or extraskeletal chondrosarcomas; these are usually pleomorphic tumors that can behave very poorly. If the excisional biopsy is found to contain high grade malignant tissue, a wide re-excision should be done after preoperative chemo-radiotherapy. All high grade malignant biopsies should have the wide excision delayed until after preoperative (neoadjuvant) chemo-radiotherapy.
2. Careful monitoring of the tumor during preoperative chemotherapy is imperative; try to confirm the response with repeat PET scans. Limit preoperative radiation therapy to 45 Gy.
3. Continue chemotherapy for as long as the tumor is responding, by evaluating with appropriate imaging studies.

Table 2 Pre-Op Rx-induced necrosis and survival

% Pre-op therapy-induced necrosis	Relative risk of local recurrence	Relative risk of distant recurrence	10-year survival
<95%	2.5	1.9	50%
>95%	1.0	1.0	90%

High grade soft tissue sarcomas: effect of preoperative-therapy-induced necrosis on survival and local control. A good response (>95% necrosis) predicted a better survival and better local control rate in high grade soft tissue sarcomas

4. Wide local excision is done after the maximum response is achieved (or in rare cases as soon as it is determined that therapy is not very effective (or not working).
5. Follow-up postoperative chemotherapy.
6. Imaging studies for early detection of recurrences and follow up.

Although soft tissue sarcomas are a very heterogeneous group, individualized preoperative intensive therapy for the high histologic grade tumors can be carried out for each individual patient and tumor which can lead to high cure rates with the best functional results.

References

1. Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma. Pathologic aspects in 20 patients after treatment with chemotherapy, EN Bloc resection and prosthetic bone replacement. Arch Pathol 1977; 101(1): 14–18. Unique Identifier: CARC/77002911.
2. Gelbard AS, Benua RS, Laughlin JS, Rosen G, Reiman RE, McDonald JM. Quantitative scanning of osteogenic sarcoma with nitrogen-13 labeled LGlutamate. J Nucl Med 1979; 20(7): 782–784.
3. Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos AG. Primary osteogenic sarcoma: the rationale for preoperative chemotherapy and delayed surgery. Cancer 1979; 43(6): 2163–2177.
4. Rosen G, Capparos B, Huvos AG, et al. Preoperative chemotherapy based upon the response of primary tumor to preoperative chemotherapy. Cancer 1982; 49(6): 1221–1230. Unique Identifier: ICDB/82011022.
5. Rosen G, Nirenberg A. Chemotherapy of osteogenic sarcoma: an investigative method, not a recipe. Cancer Treat Rep 1982; 66(9): 1687–1697. Unique identifier: ICDB/83000286.
6. Eilber F, Eckhart J, Rosen G, Forscher C, Selch M, Fu YS. Preoperative therapy for soft tissue sarcoma. Hematol Oncol Clin North Am 1985; 9: 817–823.
7. Rosen G, Forscher C, Lowenbraun S, et al. Synovial sarcoma. Uniform responses of metastases to high dose ifosomide. Cancer 1994; 73(10): 2506–2511. May 15.
8. Kampe CE, Rosen G, Eilber F, et al. Synovial sarcoma. A study of intensive chemotherapy in 14 patients with localized disease. Cancer 1993; 72(7): 2161–2169. Oct 1.
9. Eilber FC, Rosen G, Eckardt J, et al. Treatment-induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol 2001; 19(13): 3203–3209. Jul 1.
10. Eilber FC, Rosen G, Nelson SD, Selch M, Dorey F, Eilber FR. High-grade extremity soft tissue sarcomas: factors predictive of local recurrence and its effect on morbidity and mortality. Ann Surg 2003; 237(2): 218–226. Feb.
11. Eilber FC, Eilber FR, Echkardt J, Rosen G, et al. The impact of chemotherapy on the survival of patients with high-grade primary extremity liposarcoma. Ann Surg 2004; 240(4): 686–695. Oct.
12. Eilber FC, Brennan MF, Eilber F, Eckardt JJ. Chemotherapy is associated with improved survival in adult patients with primary extremity synovial sarcoma. Ann Surg 2007; 246(1): 105–113. Jul.