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Perspectives and Commentaries

The Prognostic Significance of Response to Induction Chemotherapy in Ewing's Sarcoma

JOHN F. ENSLEY

Department of Medicine, Wayne State University, Harper-Grace Hospital, Detroit, MI 48201, *U.S.A.*

(A COMMENT ON: Oberlin O, Patte C, Demeocq F *et al.* The response to initial chemotherapy as a prognostic factor in localized Ewing's sarcoma. *Eur J Cancer Clin Oncol* 1985, **21**, 463-467.)

CONTEMPORARY lists of curable malignancies include Ewing's sarcoma, first described in 1921 by James Ewing. At the time of its initial description, and as recently as two decades ago, this highly malignant tumor was considered anything but curable. As recently as 1968, the expression "if an Ewing's is cured, it was not an Ewing's" [1] typified the futile attitude prevalent among those treating this neoplasm. Furthermore, the histogenesis of this round cell tumor of pediatric bone continues to defy resolution. Histologic features consistent with myelogenous and endothelial cell lines raise the question of whether the term 'sarcoma' should be applied to this malignancy at all. In spite of the lack of knowledge concerning the cell of origin, the etiology of the tumor and a generally accepted staging system, current treatment strategies produce 5-yr survival rates of 60% in localized Ewing's sarcoma as compared to less than 10% only a few decades ago.

Interestingly, history records that James Ewing first suggested repeated radiation treatments as a possible treatment modality [2]. In the ensuing third of a century, aggressive surgery, including amputation and limb disarticulation, replaced this conservative approach. Ultimately the metastatic nature of this tumor demonstrated the ineffectiveness of surgery alone as a primary treatment modality. By the fifth and sixth decades, radiation had again moved to the fore as the major therapeutic modality. Unfortunately, local therapy, either surgery or radiotherapy, cannot eradicate a disease that by its natural history universally presents or relapses in a disseminated fashion. Two forms of systemic therapy have been employed to date. Studies at the Princess Margaret Hospital and Hospital for Sick Children [3, 4] both reported an improvement in disease-free and overall survival using 300 cGy total-body irradiation in conjunction with local radiotherapy. Currently, chemotherapy is the predominant form of systemic therapy employed in the treatment of this malignancy. Early trials using single agents demonstrated that this tumor was responsive to chemotherapy as well as radiation. Several classes of agents have demonstrated activity in Ewing's sarcoma, including alkylating agents (cyclophosphamide), naturally occurring antibiotics (actinomycin D and adriamycin), vinca alkaloids (vincristine) and nitrosoureas (BCNU). Most combination regimens to date have employed at least two and usually three or more of these agents simultaneously.

Adjuvant chemotherapy has been employed before, during and after definitive local irradiation in the treatment of Ewing's sarcoma. These trials have clearly demonstrated that local control as well as relapse-free survival have been subsequently improved. The addition of adjuvant chemotherapy produces 90-95% local control compared to 65-75% with radiation alone. Current multimodality strategies in Ewing's sarcoma employ induction chemotherapy prior to radiation and/or surgery [5]. Such an approach may be beneficial in that: (1) one is able to observe the efficacy of cytoreductive regimens used; (2) less volume or dose of radiation may be employed, or local surgery may replace radiation in some cases; (3) necessary reductions in chemotherapeutic dosage may be avoided when radiotherapy is given concomitantly; (4) the loss of bone marrow reserve that may preclude the use of adequate

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chemotherapy when large volumes of tissue are irradiated may be avoided; (5) the effectiveness of radiation may be increased following reduction in tumor size. One of the most compelling arguments for the use of induction chemotherapy is that the initial response may prove of prognostic importance in Ewing's sarcoma as it has in other tumors.

In an article recently published in this journal, Oberlin *et al.* [6] report a trial of the French Pediatric Society which looks specifically at the prognostic importance of tumor response in 67 patients with localized Ewing's sarcoma who had measurable soft tissue masses or functional symptoms. These patients were treated with alternating VAC (vincristine, actinomycin D, cyclophosphamide) and VAd (vincristine, adriamycin combinations) until maximum tumor reduction or complete response occurred. Following induction chemotherapy, patients underwent irradiation of the entire involved bone. Six weeks following radiotherapy, maintenance chemotherapy was begun, consisting of alternating VAC and VAd until cumulative doses of adriamycin reached 480 mg/m^2. Following this, maintenance was continued for a total of 16 months with VAC alone. Response was divided somewhat unconventionally into good responders and bad responders. Good responders (41/67, 61%) were defined as achieving either a classical complete remission or having only minimal residual disease. In addition, these patients had complete disappearance of all functional symptoms. Bad responders (26/67, 39%) either had less than a 50% reduction in tumor size (7), grew in size (4), remained stable (5) or had only transient tumor reduction (10). All bad responders had persistent or recurrent functional symptoms. With a median follow-up of 36 months, the 4-yr disease-free actuarial survival for the entire group was 52.1%. The difference in disease-free survival between good and bad responders was highly significant: 57.3 vs 9% ($P < 0.00001$). Importantly, the only patients (3) who failed to achieve a complete remission following radiation were found among the bad responders. Equally as important was the observation that 23 of the 26 bad responders achieved a complete remission with radiation, but subsequently 16 relapsed (4 local and 12 distant metastases). Therefore the initial response to chemotherapy was not only prognostically important in terms of survival but had implications for the subsequent effectiveness of radiotherapy.

The attainment of a complete clinical response is the first goal in the treatment of malignancies not curable with local therapy. This has been a cornerstone in the evolution of successful treatment regimens for each of the following neoplasms now considered curable: Hodgkin's disease, acute lymphocytic leukemia of childhood, choriocarcinoma, diffuse histiocytic lymphoma, testicular carcinoma, ovarian carcinoma, Wilm's tumor, Burkitt's lymphoma and embryonal rhabdomyosarcoma [7]. Recent reports have confirmed the value of adjuvant chemotherapy in soft tissue sarcomas [8] and have questioned the value of such therapy in osteogenic sarcoma [9]. Serious questions have been raised, particularly in reference to osteogenic sarcoma trials, concerning the use of historical controls. Many of these same concerns can be applied to the improved survival that has occurred in Ewing's sarcoma. Improved techniques of diagnosis and detection of metastatic disease, better patient selection and medical support have contributed to the improved survival seen with this tumor in modern treatment trials. Nevertheless, the impact of improved radiotherapy techniques and dosage and the addition of adjuvant chemotherapy cannot be denied. Therefore randomized trials without these improvements would not be ethical.

Advanced squamous cell cancer of the head and neck, a tumor that as yet has not attained the curable status of Ewing's sarcoma, has many parallels with regard to the prognostic importance of response to induction chemotherapy. In the advanced, unresectable state, these tumors have been uniformly fatal. Over the last decade combination chemotherapy regimens have been employed prior to irradiation or surgery much as it is employed in Ewing's sarcoma, in an attempt to improve survival and ultimately produce cure. The attainment of a complete clinical response with chemotherapy in these trials has been predictive of improved survival for such patients [10]. Additionally, sequential response patterns between chemotherapy and radiotherapy indicate that the response to induction chemotherapy is predictive of further response to radiation [11]. Furthermore, the attainment of a complete remission following radiotherapy offered no survival advantage in patients who were not complete responders following chemotherapy [12]. Similar trends are evident in the induction chemotherapy trial of Ewing's sarcoma reported by Oberlin *et al.*, although the definitions of response and the chemotherapy-radiotherapy response relationships are less precise.

Without randomized, prospective, controlled clinical trials, the survival advantage seen in such patients achieving a complete response to chemotherapy may be viewed with suspicion. It may be argued that such patients would have

survived longer regardless of therapy and that the response to chemotherapy merely identified this good prognostic group. It may also be argued that the increased efficiency of the radiotherapy following successful debulking chemotherapy may be the real cause of the survival advantage observed. Since it is likely that future trials of Ewing's sarcoma will employ combination chemotherapy in an adjuvant fashion prior to radiation, it should be possible to further examine this question.

Currently, the accepted clinical parameters of prognostic importance in Ewing's sarcoma include the site of tumor growth, the presence of distant metastasis, the degree of soft tumor involvement, the histological pattern, the size of primary, the presence of functional or constitutional symptoms and the elevation of serum lactate dehydrogenase [13, 14]. If the observations of Oberlin *et al.* are confirmed in these future trials, the prognostic importance of initial response to combination chemotherapy in Ewing's sarcoma may be added to the list.

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