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The Response to Initial Chemotherapy as a Prognostic Factor in Localized Ewing's Sarcoma

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For the French Society of Pediatric Oncology

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Abstract—*Ninety-five children with localized Ewing's sarcoma were included in a prospective cooperative study. All patients received initial chemotherapy with the purpose of early prevention of metastases and improvement of the conditions of the subsequent local therapy, radiotherapy in all cases, surgical resection in selected cases. Clinical response to initial chemotherapy was evaluated in 67 patients who had measurable soft tissue mass or functional symptoms. This response appeared highly correlated with outcome as the disease-free survival was 57.3% for the 41 good responders and 9% for the 26 bad responders ($P < 0.00001$), though 23 of these bad responders reached complete remission with radiotherapy. This study also confirms the prognostic significance for survival of the site of the primary tumor on axial skeleton or on limbs. Nevertheless, this factor had no predictive value for response to chemotherapy, which thus appears to be an independent factor.*

INTRODUCTION

SINCE 1970 the starting of adjuvant chemotherapy concomitantly with radiation therapy has greatly increased the long-term survival of patients with localized Ewing's sarcoma.

In 1978 the French Society of Pediatric Oncology initiated a new protocol based on a combined chemotherapy which was started as soon as possible after biopsy. The purpose of this early use of effective drugs was to prevent metastatic spread and to improve the conditions of local therapy; this procedure allowed reduction of the tumor volume to be irradiated and enabled certain patients to undergo surgery.

The data reported here show that the response to primary CT is reflected by survival.

MATERIALS AND METHODS

By May 1984, 110 patients were included in the cooperative study of the French Society of Pediatric Oncology, 95 of them had localized Ewing's sarcoma. Their ages ranged from 2.5 to 21.5 yr (median: 10 yr). Diagnosis was made by surgical biopsy. All histological samples were later re-examined by the same team of pathologists.

The distribution of primary sites is shown in Table 1.

Pretreatment investigations consisted of complete clinical and radiological examinations, bone scan for all patients and computerized tomography for most of the patients with pelvic or costal lesions. Special attention was paid to evaluating the size of the tumor mass.

For therapeutic purposes, we identified two groups of patients according to the extent of the disease: (a) those with 'small tumors', mostly situated on the limbs with little or no soft-tissue mass and (b) those with 'large tumors' mostly on axial bones including primary rib tumor with pleural involvement.

Group (a) patients were given two courses of VAC (vincristine, actinomycin, cyclophosphamide) beginning on days 1 and 22, and group (b) were given alternating VAC and VAd (vincristine,

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Table 1. Distribution of primary Ewing's sarcoma in 95 patients

Pelvis	14	Femur	16
Sacrum	7	Tibia	11
Vertebrae	2	Fibula	7
Rib	14	Humerus	11
Scapula	5	Ulna	2
Mandibula	1	Radius	2
Clavicle	1		

adriamycin) until maximum tumor regression (i.e. complete remission or no further progressive reduction); see Fig. 1 [1].

The clinical response to chemotherapy was evaluated after each course and particular attention was given to functional symptoms such as pain or nervous compression.

On completion of the initial chemotherapy sequence each patient was re-evaluated by clinical examination, radiography and/or CT scan (depending on the initial investigations) and was then classified as a good or bad responder.

After the induction chemotherapy patients underwent irradiation of the entire bone. During radiation therapy chemotherapy consisted of two cycles of vincristine + adriamycin on days 1 and 22, followed by two cycles of vincristine + cyclophosphamide on days 53 and 74.

Maintenance CT began 6 weeks after radiotherapy. It comprised alternating VAC and VAd until the cumulative dose of adriamycin reached 480 mg. VAC was then administered alone until completion of 16 months of therapy.

The survival date was taken as May 1984, so that the median follow-up was 3 yr. Actuarial curves were plotted according to the Kaplan-Meier method and compared using the log-rank test [2].

RESULTS

Response to primary chemotherapy (Table 2)

Twenty-eight of the 95 patients with localized disease could not be evaluated for response to CT for the following reasons: six had surgical tumor resection at diagnosis (rib in four cases, fibula in one, clavicle in one); 20 had no measurable soft-tissue mass; one patient underwent RT after the first cycle of CT; and one was deviating from the protocol.

Table 2. Response to primary chemotherapy in the 67 patients who could be evaluated

Good responders ($n = 41$)
14 complete remission
27 minimal residual mass (greater than 50% regression)
Bad responders ($n = 26$)
4 progressive disease
5 stable disease
7 moderate regression of tumor (less than 50%)
10 transient efficiency of chemotherapy

Forty-one patients of the 67 who could be evaluated (61%) were considered as 'good responders': 14 of them attained complete remission with complete disappearance of soft tissue mass and improvement in bone lesions and 27 exhibited a large reduction of their soft tissue mass but a minimal residual mass persisted. In all of these cases functional symptoms disappeared swiftly.

Twenty-six patients were considered as 'bad responders' (39%): the tumor grew during therapy in four children, remained stable in five and showed a moderate reduction (less than 50%) in seven. In ten patients the tumor began to shrink after the first cycle of chemotherapy and although functional symptoms rapidly improved, pain, inflammation or paralysis re-appeared a few days before the subsequent cycle without palpable recurrence of the soft tissue mass. When such transitory efficiency was noted after the first cycle, it was often observed again after the next, even when different drugs were given.

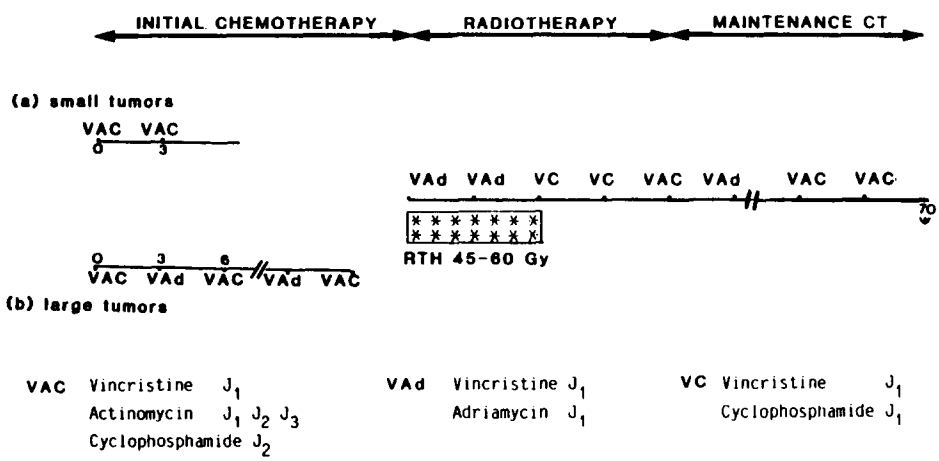

Fig. 1. Schedule of the therapy. V = vincristine 1.5 mg/m², *A = actinomycin D* 25 μg/kg, *C = cyclophosphamide* 1.5 g/m², *Ad = adriamycin* 60 mg/m².

Correlation of response to CT and outcome

In May 1984 the 4-yr survival level of the entire group of patients was 56.2% and the disease-free survival 52.1% (the three patients who never achieved disease-free status are considered to have relapsed during the first month) (Fig. 2).

Judging from the response to chemotherapy, good responders survived longer than bad responders: 28 of the good responders (68%) still survived disease-free while seven of the bad responders (27%) were disease-free. Among these seven patients, six had a follow-up shorter than 14 months and are still on therapy. The difference in disease-free survival between the two groups is highly significant (57.3 vs 9.0%, $P < 0.00001$; Fig. 3). The disease-free survival of the 28 patients who could not be evaluated for their response to chemotherapy is 79.2%.

Of the three bad responders who had no complete remission, one died of regional progressive disease and the two others developed metastases within a few weeks. All of the 23 other patients who were considered as chemotherapy failures attained complete remission by radiotherapy but 16 of them relapsed. It is noteworthy that these relapses were local recurrences for four patients but distant metastases for 12. This

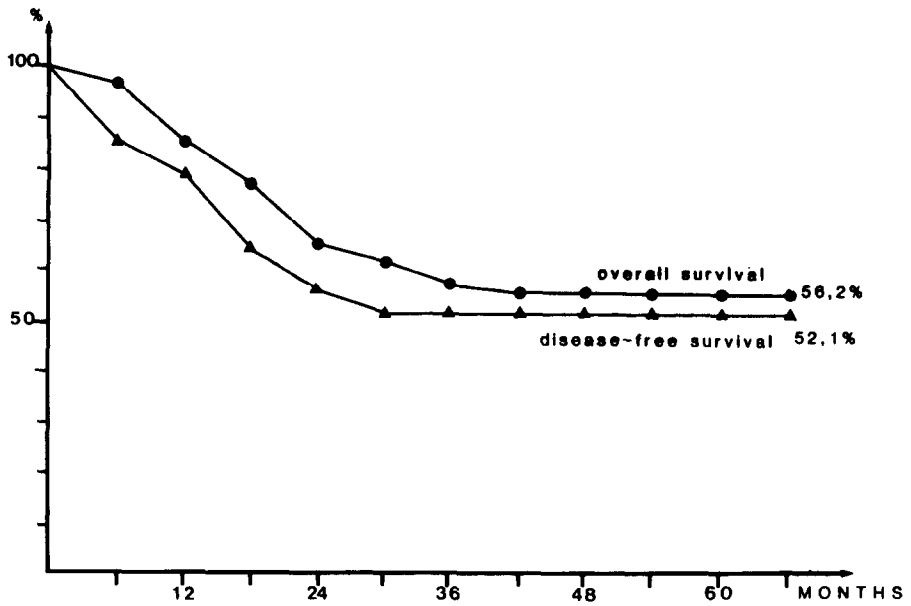

Fig. 2. Actuarial overall and disease-free survival in 95 patients with localized Ewing's sarcoma.

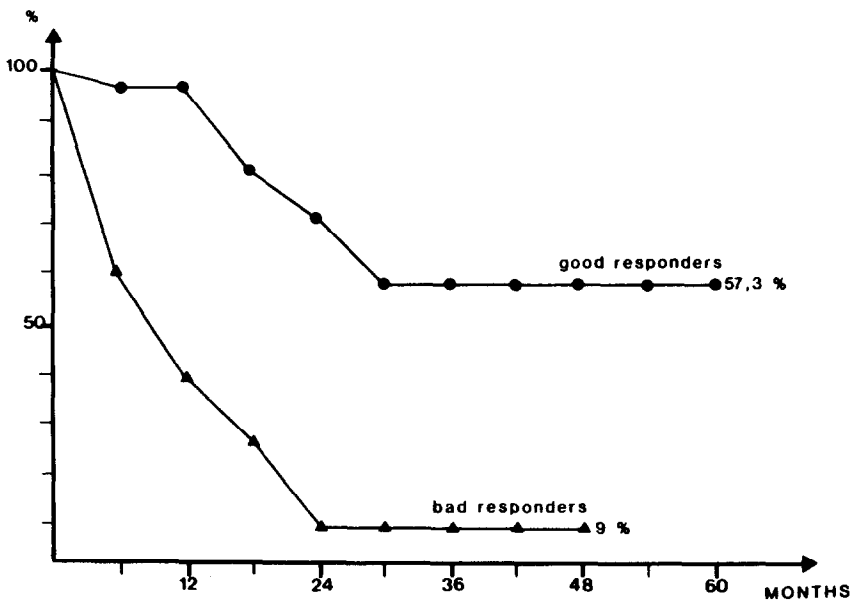

Fig. 3. Actuarial disease-free survival according to the response to initial chemotherapy: good responders, n = 26; *bad responders,* n = 41.

pattern of relapses did not differ from the pattern for the good responders (Table 3).

On the other hand, the median time of relapse (local recurrence or metastases) differed significantly in the two groups: 8.7 months for the bad responders and 17.3 months for the good responders ($P < 0.001$).

Correlation of response to chemotherapy with other prognostic factors

The site of the primary tumor (on axial skeleton or on limbs) has been shown to be a prognostic factor for survival [3]: in our study 19 of the 44 patients with axial lesions (43%) and 39 of the 51 patients with lesions on limbs (76%) remained free of disease. The difference in disease-free survival is statistically significant ($P < 0.005$).

Nevertheless, the site of tumor (axial bones or limb bones) has no predictive value for the response to chemotherapy (Table 4). Therefore the site of primary tumor and the response to chemotherapy appear to be two independent prognostic factors, and after adjustment for the primary tumor site, the response to chemotherapy remains highly correlated with survival ($P < 0.00001$).

DISCUSSION

This follow-up of 95 patients with localized Ewing's chemotherapy has a significant connection with disease-free survival.

It also suggests that for the 'bad responders' to chemotherapy who nevertheless attain complete remission with radiotherapy, their risk of subsequent relapse is as much distant metastases as local recurrence. These results suggest that the treatment of these patients should be based on local radiotherapy as well as on systemic chemotherapy.

Though our results are based on a large number of patients, they are related to only one schedule of chemotherapy and other groups may have a different experience. Hayes *et al.* reported, in their first article on the response of Ewing's sarcoma to moderate-dose CT, that all their patients but one exhibited either complete or more than 50% regression of soft tissue tumors [4]. This outcome may be in connection to kinetics for drug administration which differs markedly from our protocol.

Although other teams have been using induction chemotherapy for several years [5, 6], as far as we know no other data have yet been published on the clinical effectiveness of this chemotherapy and its correlation with the outcome.

It seems to us that further very careful studies are warranted to confirm this finding, which appears to be a very strong prognostic factor.

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Table 3. Evolution according to response to chemotherapy

	No complete remission	Local recurrence	Metastasis	Disease-free survivors
Bad responders ($n = 26$)	3	4	12	7
Good responders ($n = 41$)		4	9	28

Table 4. Response to chemotherapy according to site of the primary tumor (%)

	Axial bones ($n = 44$)	Bones of limbs ($n = 51$)
Not measurable	27	32
Good responders	41	45
Bad responders	32	23

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