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Analysis of a series of sixty soft tissue sarcomas in adults treated with a cyclophosphamide-vincristine-adriamycin-dacarbazine (CYVADIC) Combination

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Summary. From 1976 to 1983, a group of 60 adult patients presenting with metastatic and/or locally advanced soft tissue sarcomas was treated with combination chemotherapy consisting in cyclophosphamide, vincristine, adriamycin, and DTIC (CYVADIC). A tumor response was obtained for 29 patients (48.3%), with 4 (6.7%) cases of complete regression. The median duration of the response was 10 months. Responses were noted in 14/22 patients receiving induction chemotherapy for advanced, and previously nonirradiated, primary tumors; among the patients with metastatic disease tumor regression was recorded in 17/32 patients with pulmonary metastases, but in none of the patients with metastases at other sites. Moreover, the attainment of a response was found to correlated with the patient's general condition, while response duration depended on the histoprognostic grade of the tumors.

Introduction

In the last decade, no new antineoplasic medication has proved to be definitely superior to Adriamycin in the chemotherapy of soft tissue sarcomas in adults, and no drug combination has given a better rate of response than CYVADIC [5].

Therefore, CYVADIC remains a reference chemotherapy, even though the results obtained by its initiators have not been reproduced by other authors [4, 6, 8, 9]. Our previous work in the field [1] is, therefore, reexamined with a study on a series of 60 patients.

Patients and methods

Patients. From January 1976 to December 1983, CYVADIC therapy was given to 63 patients suffering from malignant soft tissue tumors. Three of these patients were not eligible for evaluation: one died during the first cycle of treatment, and in the other two the pathological review was unable to confirm the initial diagnosis of a sarcoma. Thus, this evaluation refers to 60 patients.

The patients were 34 men and 26 women, with an age range of 18–79 years (median: 45 years). None presented with any serious visceral defect; cardiopathy, which would have contraindicated the use of Adriamycin, was checked for with particular care. The Karnofsky index was 70% or more for 46 patients, and less than 70% for 14.

The histological types of sarcoma encountered are shown in Table 1. Of the 11 recognized morphological types, 5 (rhabdomyosarcoma, fibrosarcoma, malignant histiocytofibroma, leiomyosarcoma, synovialosarcoma) accounted for at least 10% of the patients, while 13 patients (21.7%) presented with unclassifiable lesions. The histoprognostic grade of the lesions at the initiation of chemotherapy was determined for 43 patients according to criteria described elsewhere [15]. Four had grade I lesions; 12, grade II lesions; and 27, grade III lesions.

There were 38 patients with pulmonary metastases, which were associated with a pleural effusion in 2 patients and with metastases at orther sites in 4; bony metastasis was present in 4 patients; 2 patients exhibited peritoneal seeding, which was associated with hepatic metastasis in 1 of them. Moreover, it must be noted that 15 patients in this

Table 1. Response to chemotherapy according to histological type

Histological types	Number of patients	Number of responses
Fibrosarcoma	9	5
Rhabdomyosarcoma	9	4
Leiomyosarcoma	6	1
Synovialosarcoma	6	4
Malignant fibrous histiocytoma	6	4
Liposarcoma	4	1
Hémangiosarcoma	2	1
Malignant schwannoma	2	1
Angiosarcoma	1	1
Clear cells sarcomas	1	0
Fusiform cells sarcomas	4	0
Alveolar sarcomas	1	0
Indifferentiated sarcomas	9	7
Total	60	29 (48.5%)
Histological grades		
Grade I	4	1
Grade II	12	6
Grade III	27	15
Unknown grade	17	7

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subgroup had signs of tumor progression at the site of their primary lesions, which were in irradiated areas in 9 cases.

In 22 patients with no known metastatic disease chemotherapy was administered to deal with a primary tumor or a local recurrence, whose locoregional extent did not allow satisfactory conservative surgical and/or radiotherapeutic treatment. Of these patients, 5 had tumors in the head and neck area; 8 patients had pelvic tumors (5 of which were uterine sarcomas); 3 had tumors of the extremities; 2 had retroperitoneal tumors; 1 patient had a sarcoma of the chest wall; another presented a mesenteric lesion and two sarcomas of the extremities.

The treatment used was the quadruple combination of cyclophosphamide 750 mg/m^2 on day 3, vincristine 1.5 mg/m^2 on day 1 (max. dose 2 mg), adriamycin (doxorubicin) 50 mg/m^2 on day 2; and dacarbazine (DTIC; 400 mg/m^2) on days 1, 2 and 3, and at 9.3 weeks. In patients with metastatic disease chemotherapy was discontinued when the patients exhibited tumor progression, except in the cases where side effects warranted its termination sooner. Adriamycin was stopped once a total dose of 550 mg/m^2 was reached. It should be noted that seven patients with pulmonary lesions underwent uni- or bilateral thoracotomy after two or three cycles of chemotherapy. The patients with nonmetastatic, locally advanced tumors were given chemotherapy as part of a therapeutic program which is detailed elsewhere [10]: Briefly, this consisted in induction chemotherapy with two to five cycles of CYVADIC, followed by a locoregional treatment with surgery and/or radiotherapy, and then further chemotherapy, for those patients in whom it had proved effective, with total doses of up to 550 mg/m^2 adriamycin. Only two patients in this series had previously undergone chemotherapy.

Monitoring. Each cycle of chemotherapy was preceded by a clinical examination, and when necessary radiological films were taken (thoracic radiography, CAT scan, tomography and/or others); hemogram, renal and hepatic tests, and electrocardiogram were routinely done. The criteria of analysis of toxicity and efficacity were those usually used in therapeutic trials in our institution and have been detailed elsewhere [3]. A tumor response was defined as a reduction of at least 50% in the product of the two largest diameters for all the tumors over a period of at least 2 months. For patients who underwent further surgery or radiotherapy evaluation of the tumor response to chemotherapy was made before this treatment.

Results

Tolerance

In terms of hematologic toxicity, 4 patients had symptomatic episodes of medullary aplasia, with infectious complications necessitating intensive hematologic reanimation. In these 4 cases, poor medullary tolerance led to discontinuation of the chemotherapy after two, two, four and eight cycles. Moreover, 16 patients suffered periods of leukopenia and/or thrombopenia persisting until the 21st day and necessitating dosage reduction by between 25% and 50%.

Digestive tolerance was also poor. The extent of vomiting led either to discontinuation to dosage reduction of dacarbazine in 5 patients, while 1 patient refused further treatment. However, the improvement in symtomatic treatment, and especially the use of high-dose metoclopramide [2], reduced the incidence of side effects of this kind.

Subtotal or total alopecia was also seen in all cases. All patients presented a moderate deterioration in their general condition, but weight loss in this series never reached more than 10% of the initial body weight. One patient had a cardiomyopathy caused by Adriamycin after a total dose of 550 mg/m^2; in addition, precordialgia occurred in one patient in the second cycle of chemotherapy without any electrical modification, and chemotherapy was therefore stopped although it was not clear that it had caused the symptoms. Electrocardiographic modifications (inversion of the T wave in precordial derivations) were noted in one other patient but had no effect on treatment.

In summary, there were no deaths associated with the treatment. However, the toxicity of the combination under study must be considered high; it is dominated by hematologi toxicity, which was observed in one out of three patients, and by constant gastrointestinal side effects, which were serious in 10% of the patients. In fact, the treatment had to be stopped in six patients (10%) in this series owing to intolerance.

Effictiveness

Tumor regression by at least 50% was noted in 29 patients in the series, out of 60 treated and analyzed; this represents a 48.3% response rate. However, complete remission attributable to chemotherapy alone was rare and was encountered in 4 patients (6.7%) only. Moreover, in 2 other patients whose tumors, measurements remained unchanged during chemotherapy, histological analysis of the surgically removed tissue revealed subtotal tumor destruction. The median duration of the effect of chemotherapy referred only to patients who did not undergo surgery or complementary radiotherapy was 10 months (3 months to 72+ months). Five patients had tumor reduction by less than 50%. For the other 24, disease progression continued during chemotherapy.

A tumor response was obtained in 27/46 patients (55.1%) with a Karnowsky index equal or superior to 70%, and was observed only in 4 out of 14 patients (28.6%) with a Karnowsky index lower than 70% ($P = 0.05$).

Table 1 shows the responses and failures of CYVADIC in relation to the histological type. It is of note that a response was recorded for only one out of six leiomyosarcomas, even though the low number of patients under study makes it difficult to obtain statistically significant results. With reference to the histoprognostic grade of the lesions, only one in four patients with grade I tumors responded to chemotherapy. The response rate for grade II and III lesions, and for those of unspecifiable grade, is essentially identical. A difference was seen, however, in the duration of response; the median duration was only 6 months for grade III tumors, while it was 12 months for grade II or unspecifiable tumors ($P = 0.035$).

If chemotherapeutic results are considered in relation to the tumor targets under treatment, a good efficacy was encountered for isolated primary tumors (14/22) and for cases in which metastasis affected only the lungs (10/17). In patients with pulmonary metastasis and signs of evolution at the primary site, the response rate remained appreciable (7/15). On the other hand, none of the patients with

metastases in extrapulmonary sites showed any response to chemotherapy.

The median survival of patients who had responded to CYVADIC and who had received no other surgical or radiotherapeutic treatment was 15 months. The median survival, once this chemotherapy no longer produced any effect, was 5 months (range: 1–18 months), which is very close to the spontaneous life expectancy of patients suffering from metastatic sarcoma. It is also very close to the median survival of patients who did not respond to treatment, which was 7 months (range: 2–42 + months). These data may indicate that the slower evolution recorded in patients who responded to the treatment can be attributed to this.

Discussion

The effectiveness of chemotherapy in adult soft tissue sarcomas is still disputed. The response rates obtained with the CYVADIC combination, which in the hands of the team that first conceived the treatment has yielded the best results published so far [6, 7, 12] could not always be reproduced [4, 6, 8, 9]. However, the treatment regimens used have varied widely, especially in dosage in each cycle and frequency of the courses [4, 6, 13]. These variations may explain, at least in part, the differences in the response rates obtained, since there is a relationship between doses of the drugs used and tumor response the case of sarcomas, particularly for Adriamycin [11].

The 3-day chemotherapeutic schedule used was similar to that used by other workers [13] to reduce the problems of treatment, but, in the present study it was delivered every 3 weeks. The response rate of 48.3% obtained in this series of 60 patients confirms the data previously reported in a smaller number of patients [1] and is comparable to that of Yap et al. [16]. However, the complete response rate is much lower (6.7% vs 17%), and the duration of response was relatively short, with a median of 10 months.

Some variables pertaining to the patient and to the illness were found to influence response to chemotherapy. The first is the patients general condition, and this is confirmed by a recently published EORTC cooperative study [13]. Some histological factors were also found to be correlated with the response to treatment. It has been reported that the response rate could vary from 23% to 60% according to the anatomopathological type of tumor [16]. However, in this series the numbers in each pathological group are too small to extrapolate significant statistics; moreover, the degree to which different anatomopathologists differ in typing tissue sarcomas does not facilitate the verification of such data [15]. The close relationship of the histological type with other factors, which could also influence the response to therapy, should also be noted. For example, the six leiomyosarcomas in this series, among which only one response was observed, presented with extrapulmonary metastatic localizations, another factor conditioning response to therapy in this series. This led us to consider the quantitative and qualitative differences of the responses according to histoprognostic grade. Only one response was obtained in four grade I lesions; moreover, while effectiveness of treatment was as frequently observed in patients with grade II as with grade III lesions, the duration of response was significantly longer in patients with grade II tumors.

Another point, the good responsiveness to chemotherapy of primary, nonirradiated tumors, should be stressed [10]. Of the 22 patients who received CYVADIC as initial treatment, 14 attained a tumor response allowing conservative locoregional treatment, which otherwise would have been impossible; in two other patients, in whom clinical and radiological results were less satisfactory, histological analysis of the surgically removed tissue revealed subtotal tumor destruction.

In summary, in this study CYVADIC is confirmed as an efficient chemotherapy for adult soft tissue sarcomas. It could be also a decisive element for control of nondisseminated primary tumors whose initial extensions do not allow a satisfactory locoregional treatment at the onset. The results could also justify the use of CYVADIC as adjuvant treatment for patients with poor prognostic sarcomas [14]. However, the low complete regression rate and the short duration of response must lead to a search for other combinations, in which Adriamycin will surely remain the principal drug.

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