Eur J Cancer Clin Oncol, Vol. 18, No. 1, pp. 33–36, 1982.
Printed in Great Britain.

0277-5379/82/010033-04$03.00/0

Combination Chemotherapy (CYVADIC) in Metastatic Soft Tissue Sarcomas

CONSTANTINE P. KARAKOUSIS*†, UMA RAO‡ and HYUNG C. PARK§
*Departments of *Surgical Oncology, ‡Pathology and §Radiology, New York State Department of Health, Roswell Park Memorial Institute, Buffalo, New York* 14263, *U.S.A.*

Abstract—*Forty-one patients with metastatic sarcoma were treated with Adriamycin,* 50 mg/m^2 *i.v. on day* 1, *Cyclophosphamide,* 500 mg/m^2 *i.v. on day* 1, *Vincristine,* 1 mg/m^2 *i.v. on days* 1 *and* 5, *and Dacarbazine (DTIC),* 250 mg/m^2 *i.v. on days* 1–5 *(CYVADIC). Three patients had a complete regression, while* 8 *patients had a partial regression of greater than* 50%. *The combined response rate was* 27%. *Eight additional patients showed stabilization of disease for an average of* 5 *months while* 22 *patients progressed on CYVADIC. Ultimately,* 7 *patients with initial tumor regression had progression of their disease. Four patients with partial regression had excision of the regressed nodules of tumor and continued on chemotherapy for a year. They remain alive at a median follow-up of* 24.5 *months, suggesting that removal of partially regressed nodules may improve results.*

INTRODUCTION

THE INITIATION of Adriamycin in clinical practice was a major advance in the treatment of metastatic soft tissue sarcoma. This drug, used alone, had produced response rates of 27–40% [1–3], while the combination of Adriamycin and DTIC (A-DIC) has been reported to produce a response rate of 42% [3].

Combination protocols with Adriamycin and Methotrexate have resulted, generally, in lower response rates of 10–36% [4–6]. The combination of Adriamycin with other drugs, in other series, resulted in varying response rates of 26–44% [7].

On the other hand, the addition of Vincristine and Cyclophosphamide to A-DIC further increased the response rates to the level of 50–60% [3, 8].

While the chemotherapy of soft tissue sarcomas has made advances with combination protocols using Adriamycin with other drugs [9], the most effective protocol is still generally considered to be CYVADIC, a combination of Adriamycin, Cyclophosphamide, Vincristine and Dacarbazine (DTIC) [10].

Accepted 27 July 1981.
†Correspondence or reprint requests to: C. Karakousis, M.D., Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263, U.S.A.

In the following, the results of treatment with this protocol in 41 patients with metastatic soft tissue sarcomas are presented.

MATERIALS AND METHODS

Forty-one patients with metastatic sarcoma having measurable disease were treated with CYVADIC, consisting of Adriamycin 50 mg/m^2 i.v. on day 1, Cyclophosphamide 500 mg/m^2 i.v. on day 1, Vincristine 1 mg/m^2 i.v. on days 1 and 5 and Dacarbazine (DTIC) 250 mg/m^2 i.v. on days 1–5. There were 22 males and 19 females in this group. The mean age of these patients was 49 yr (range 22–71 yr). There were 18 patients with leiomyosarcoma, 5 with rhabdomyosarcoma, 5 with liposarcoma, 5 with malignant fibrohistiocytoma, 2 with hemangiosarcoma, 2 with unclassified sarcoma, 2 with fibrosarcoma and 2 patients with alveolar cell sarcoma and epithelioid sarcoma respectively.

At the time of initiation of chemotherapy with CYVADIC, 13 patients had metastatic lesions involving the lungs exclusively, 3 had pulmonary as well as other metastases, seven patients demonstrated hepatic and other metastases, 8 patients had intraperitoneal seeding, 6 patients had locally unresectable or residual tumor, 3 patients had metastases to lymph nodes and 1 patient osseous metastases. They all were evaluable and demonstrated a mini-

mum survival of 3 months following the initiation of chemotherapy with CYVADIC. Ten patients who had early deaths or were lost to follow-up were excluded from consideration in this study.

The number of courses given varied from 1 to 21, with a mean of 4.5 courses. A single course was given only in patients with unequivocal, substantial tumor progression following the first treatment.

RESULTS

Moderate hematopoietic toxicity (WBC 2000–3000/mm^3), requiring a 25% dose reduction, occurred in 9 patients, while more severe toxicity (WBC 1000–2000/mm^3), requiring a 50% dose reduction, occurred in 5 patients. There was no fatal toxicity. Four patients had peripheral numbness, which led to discontinuation of Vincristine. There was one incidence of cardiac toxicity in a 58-yr-old man with pulmonary metastases from rhabdomyosarcoma, who presented evidence of congestive heart failure after 5 courses of CYVADIC and died later as a result of tumor progression.

Three patients had complete clinical regression, which was followed later by recurrence in all of them. One of these patients, a 67-yr-old woman with an unresectable retroperitoneal leiomyosarcoma in the area near the retrohepatic portion of inferior vena cava, had a complete clinical regression on the basis of her CT scan which lasted 30 months. A 65-yr-old man with unresectable liposarcoma in the trunk had a complete regression which lasted 12 months. A 53-yr-old man with unresectable liposarcoma in the area of the lower neck and mediastinum had a complete regression which lasted 29 months.

Eight patients had greater than 50% regression in the size of their tumor. Of these, 3 had metastatic leiomyosarcoma, 1 to liver and the paravertebral area, 1 to the lungs and 1 had unresectable tumor in the retroperitoneum as well as malignant ascites. Two patients had metastatic rhabdomyosarcoma, 1 with lymph node metastases to right axilla and left groin and 1 with regional recurrence. Two had malignant fibrohistiocytoma, 1 metastatic to the lungs and 1 in retroperitoneal area of left flank. The eighth patient had a fibrosarcoma metastatic to the lungs. The duration of response in 4 of these patients treated only with chemotherapy was 4, 4, 5 and 8 months. Of the remaining 4 patients, the patient with retroperitoneal leiomyosarcoma and malignant ascites had disappearance of his ascites after the first course of chemotherapy. His mass regressed by more than 50%, but after the third course no further regression was noted. Six months after initial admission the residual retroperitoneal tumor was removed and splenectomy, distal pancreatectomy and partial gastrectomy were carried out. The residual mass of tumor measured 15×12.9 cm. There was marked hyalinization and degenerative changes in the tumor cells, probably secondary to chemotherapy. The patient received 6 more courses of chemotherapy and 19 months after tumor resection he was free of recurrence. The 3 other patients, with leiomysarcoma (simultaneous presentation of primary and metastatic disease), fibrohistiocytoma (5 months after excision of the primary) and fibrosarcoma (11 months after excision of the primary) metastatic to the lungs had more than 50% regression after 2 courses of chemotherapy and then underwent median sternotomy and resection of pulmonary metastases. All 3 patients completed one year of chemotherapy. One was alive with disease at 18 months of follow-up, while the other 2 were alive and disease-free at 24 and 30 months respectively. Eight patients had stabilization for 4–8 months (mean 5 months).

Progression of disease occurred in 22 patients after one, two or three courses in 9, 6 and 7 patients respectively.

The 3 patients with complete regression had a median survival from initiation of CYVADIC of 33 months with a range of 29–47 months.

The 8 patients with partial objective regression had a median follow-up of 21 months. The 4 patients who had chemotherapy only had a median survival of 10.5 months, with a range of 6–24 months. The 4 patients with combination surgery and chemotherapy had a median follow-up of 24.5 months (range 18–30 months) and were all alive at this time, 3 free of disease.

The 8 patients with stabilization had a median survival of 12 months, with a range of 7–30 months.

Twenty-two patients with progression had a median survival of 4.0 months, with a range of 3–9 months.

Of the 11 patients with objective regression, 7 patients had myelosuppression, requiring modification of the dose by 25% in 6 patients and 50% in 1 patient. Of the 8 patients with stabilization, 3 had hemopoietic toxicity, and of the 22 patients with progression, only 4 exhibited such toxicity. The rate of hemopoietic toxicity observed among patients with objective regression was significantly higher than that observed among patients with progression ($P < 0.05$).

DISCUSSION

The combination of Cyclophosphamide, Vincristine, Adriamycin and Dacarbazine (DTIC) is still generally considered to provide the best response rate in soft tissue sarcoma [8–10]. The highest objective response for this combination in a large series was that by Gottlieb *et al.*, who reported a response rate of 59% [3]. A recent update of the experience with CYVADIC in soft tissue sarcomas, from the M. D. Anderson Hospital, still showed an objective response rate of 50% [11].

However, a response rate as low as 15% has been reported by Giuliano *et al.* [12], which suggests that the response rate of CYVADIC may ultimately prove to be in the 35–45% range [10]. A re-evaluation of the CYVADIC regimen for metastatic soft tissue sarcoma by the EORTC Group showed that there was an initial 24% response rate, at 8 weeks in the CYVADIC arm, with an overall response rate of 37% [13].

The observed objective response rate to CYVADIC was only 27% in this series. Among the 12 patients with objective regression, 7 experienced mild to moderate hemopoietic toxicity, while among 22 patients with no response, only 4 had hemopoietic toxicity as a result of the chemotherapy. This difference was statistically significant ($P < 0.05$) and suggests that chemotherapy with CYVADIC should be pushed to the point of mild toxicity.

It is interesting that of the 11 patients with objective response, all 7 patients who had no resection of the regressed site(s) progressed after a variable period. Four patients with partial regression who had these partially regressed lesions removed were all alive (3 disease-free) at a median follow-up of 24.5 months.

For most tumors complete response to chemotherapy is less common than partial response. The factors preventing a partial objective response from becoming a complete one are not well known. From a theoretical standpoint, there are two plausible explanations which in many cases may operate together. One is that, with the known heterogeneity of malignant cells in any given tumor, some cell lines may be sensitive to one or more drugs while others are not. The other explanation is that involving kinetic and perfusion aspects [14, 15]. In any macroscopic nodule the growth fraction is generally low, particularly in the center of nodules where the blood supply is inadequate [16]. According to the second explanation, partial regression occurs because the drugs destroy the sensitive cells in the periphery, while the ones in the center, being mostly in a resting phase and receiving inadequate amounts of the drug, develop resistance to them and finally begin to grow again.

It is a matter of pure speculation which of the two above mechanisms is more significant. The instances of tumor regression in some nodules, while other nodules in the same patient progress or remain stable, strongly support the explanation of cell heterogeneity. But such instances are infrequent and the usual case clinically is of partial tumor regression which ceases to regress and after several months starts to grow and disseminate again. To the extent that the second explanation, i.e., development of drug resistance in the poorly perfused areas of tumor, is valid, surgical excision of partially regressed lesions becomes sensible in order to remove tumor masses about to become resistant, hoping that microscopic metastases have been destroyed.

Removal of pulmonary metastases in soft tissue sarcomas is a well-established practice [17]. However, the success of such treatment is more likely if there has been an interval longer than one year between excision of the primary and appearance of pulmonary metastases [18, 19]. Two of our surgically-treated patients had synchronous presentation of primary and metastatic lesions, while in the other two the interval between resection of the primary and appearance of metastases was shorter than one year. The favorable experience in the present series, with these four patients who had surgical removal of residual metastatic tumor after partial regression and then continuation of chemotherapy for a year, suggests that increased palliation may be achieved by this approach.

Acknowledgement—Statistical analysis of the data was made by Mr. Robert Moore, M.S., Department of Biostatistics, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

REFERENCES

1. O'Bryan RM, Luce JK, Talley RW *et al.* Phase II evaluation of adriamycin in human neoplasia. *Cancer* 1973; **32:** 1–8.
2. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin: a new effective agent in the therapy of disseminated sarcomas. *Med Pediatr Oncol* 1975; **1:** 63–76.

3. GOTTLIEB JA, BAKER LH, O'BRYAN RM *et al.* Adriamycin (NSC-123127) used alone and in combination for soft tissue and bony sarcomas. *Cancer Chemother Rep* 1975; **6:** 271–282.
4. BULL FE, IRWIN LE, PUGH RP, BATEMAN JR. Phase I study of adriamycin–methotrexate combination in sarcomas. *Proc Am Soc Clin Oncol* 1976; **17:** 249.
5. KAUFMAN JH, CATANE R, DOUGLASS HO, JR. Combined adriamycin, vincristine, and methotrexate in advanced, adult, soft-tissue sarcoma. *NY State J Med* 1977; **77:** 742–743.
6. LOWENBRAUN S, MOFFITT S, SMALLEY R, PRESANT C. Combination chemotherapy with Adriamycin, Cyclophosphamide & Methotrexate. *Proc Am Soc Clin Oncol* 1977; **18:** 286.
7. MAGILL GB, GOLBEY RB, KRAKOFF IH. Chemotherapy combinations in adult sarcomas. *Proc Am Soc Clin Oncol* 1977; **18:** 332.
8. BENJAMIN RS, GOTTLIEB JA, BAKER LO, SINKOVICS JG. CYVADIC vs CYVADACT—A randomized trial of cyclophosphamide (CY), vincristine (V), and adriamycin (A), plus dacarbazine (DIC), or actinomycin-D (DACT) in metastatic sarcomas. *Proc Am Soc Clin Oncol* 1976; **17:** 256.
9. PINEDO HM, KENIS Y. Chemotherapy of advanced soft tissue sarcomas in adults. *Cancer Treat Rev* 1977; **4:** 67–86.
10. BRAMWELL VHC, PINEDO HM. Bone and soft tissue sarcomas. In: PINEDO HM, ed. *Cancer Chemotherapy* 1979. New York, Elsevier, 1979, 424–450.
11. YAP BS, BAKER LH, SINCOVICS JG *et al.* Cyclophosphamide, vincristine, adriamycin, and DTIC (CYVADIC) combination chemotherapy for the treatment of advanced sarcomas. *Cancer Chemother Rep* 1980; **64:** 93–98.
12. GIULIANO AE, LARKIN KL, EILBER FR, MORTON DL. Failure of combination chemotherapy (CYVADIC) in metastatic soft tissue sarcomas: implications for adjuvant studies. *Proc Am Soc Clin Oncol* 1978; **19:** 359.
13. PINEDO HM, VENDRIK CPJ, BRAMWELL VHC *et al.* Re-evaluation of the CYVADIC regimen for metastatic soft tissue sarcoma. *Proc Am Soc Clin Oncol* 1979; **20:** 346.
14. SKIPPER HE. Kinetics of mammary tumor cell growth and implications for therapy. *Cancer* 1971; **28:** 1479–1499.
15. BENDER RA, DERICK RL. Cytokinetic aspects of clinical drug resistance. *Cancer Chemother Rep* 1975; **59:** 805–809.
16. ZUBROD CG. Principles of chemotherapy. In: HOLLAND JR, FREI III E, eds. *Cancer Medicine.* Philadelphia, Lea & Febiger, 1973; 601–605.
17. HUANG MN, EDGERTON F, TAKITA H *et al.* Lung resection for metastatic sarcoma. *Am J Surg* 1978; **135:** 804–806.
18. JOSEPH WL. Criteria for resection of sarcoma metastatic to the lung. *Cancer Chemother Rep* 1974; **1:** 285–290.
19. HUTH JR, HOLMES EC, VERNON SE *et al.* Pulmonary resection for metastatic sarcoma. *Am J Surg* 1980; **140:** 9–16.