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Cyclophosphamide, Hexamethylmelamine, Adriamycin and Cisplatin Combination Chemotherapy in Mixed Mesodermal Sarcoma of the Female Genital Tract

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Abstract—*Clinically mixed mesodermal sarcoma is a different entity among the other subtypes of soft tissue sarcomas. Although adriamycin is considered to be the most active single agent in the treatment of adult soft tissue sarcomas, the drug has only limited activity in mixed mesodermal sarcomas. On the other hand, cisplatin is inactive in soft tissue sarcomas, but was reported to be active in mixed mesodermal sarcomas. Therefore combinations including both adriamycin and cisplatin appear attractive for testing in the treatment of mixed mesodermal sarcomas. We have performed a pilot study with two combinations in mixed mesodermal sarcomas of the female genital tract. Two patients treated with adriamycin and cisplatin showed rapid progression. Of 7 patients treated with cyclophosphamide, hexamethylmelamine, adriamycin and cisplatin (CHAP-5), 6 had measurable disease, of whom 5 yielded a response (2 complete responses for 19+ and 40 months and 3 partial responses for 4, 7 and 8 months). The patient with non-measurable disease had a progression-free survival of 27 months. The median survival for all CHAP-5-treated patients was 20 months. This regimen is recommended for further phase II studies.*

INTRODUCTION

MIXED mesodermal sarcomas of the female genital tract are rare tumors with an overall 5-year survival rate of 33–38% [1, 2]. For recurrent disease survival appears to be 9 months or less [3, 4].

Concerning chemotherapy in adult soft tissue sarcomas in general, adriamycin is the most active single agent, whereas for combination chemotherapy the best results have been obtained with adriamycin and dacarbazine (DTIC) or this combination plus cyclophosphamide and vincristine (CYVADIC) [5]. However, the results of chemotherapy for mixed mesodermal sarcomas are different, yielding lower response rates of 0–20% [6–9]. For mixed mesodermal sarcomas originating from the uterus a response rate of 18% was reported for cisplatin as second-line chemotherapy [10], while this drug is considered inactive in other histologic subtypes of soft tissue sarcomas [11–13]. Combination chemotherapy with cyclophosphamide, hexamethylmelamine, adriamycin and cisplatin (CHAP-5) is frequently applied in ovarian cancer. Here we present the results of a pilot study with the same regimen in mixed mesodermal sarcomas, initiated after failure of a combination of adriamycin and cisplatin in 2 patients.

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MATERIALS AND METHODS

Nine patients with histologically proven metastatic mixed mesodermal sarcomas of the female genital tract [7 uterus, 1 tuba, 1 ovary; median age 61 years (range 49–72); median WHO performance score 1 (range 0–2)] were treated. The first 2 patients received adriamycin 35 mg/m^2 i.v. and cisplatin 50 mg/m^2 i.v. on day 1, every 4 weeks. The following 7 patients were treated with the CHAP-5 regimen, consisting of adriamycin 35 mg/m^2 i.v. day 1, cisplatin 20 mg mg/m^2 i.v. days 1–5, hexamethylmelamine 150 mg/m^2 and cyclophosphamide 100 mg/m^2 p.o. days 15–28, cycles repeated every 5 weeks.

Three patients presented with metastases at the initial diagnosis, 6 developed metastases after local treatment with surgery alone (2 patients) or surgery in combination with radiotherapy (4 patients). Metastatic sites were in the lung (3 patients), skin

(1 patient) and abdomen (5 patients). Of the latter 5 patients, one did not have measurable lesions. One patient received prior chemotherapy with ifosfamide. Tumor response was evaluated by standard WHO criteria [14]: complete response was defined as the disappearance of all known disease for at least 4 weeks; partial response as a more than 50% decrease in the sum of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks; stable disease as a less than 50% decrease and a less than 25% increase in measurable or evaluable lesions; and progression as an increase greater than 25% in the size of one or more measurable or evaluable lesions or the appearance of new lesions. Duration of partial response was calculated from the time of start of chemotherapy to progression; duration of complete response was calculated from the moment complete response was achieved.

RESULTS

The first 2 patients, who were treated with adriamycin and cisplatin, both developed rapid tumor progression. The remaining 7 patients received a median of 5 cycles of CHAP-5 per patient (range 3–12). Side effects consisted of nausea and vomiting (WHO grade 3) and total alopecia in all patients. There was no serious nephrotoxicity. The median nadir of white blood cells was 1.8×10^9/l (range 1.1–2.4), the median nadir of platelets was 32×10^9/l (range 14–91). There was no sepsis nor bleeding. Platelet transfusions were not necessary. Of 6 patients with measurable disease treated with CHAP-5, 2 achieved a complete remission for 40+ and 19 months, 3 achieved a partial remission for 4, 7 and 8 months, respectively, and one had stable disease for 5 months, after which metastatectomy was performed. The patient with unmeasurable disease was treated with six cycles of CHAP-5 after incomplete debulking surgery and had a progression-free survival of 27 months. In all CHAP-5-treated patients median survival was 20 months (range 8–67 months).

DISCUSSION

Clinically mixed mesodermal sarcoma from the female genital tract is a different entity among the other subtypes of soft tissue sarcomas. Adriamycin is the most active single agent in the treatment of adult soft tissue sarcomas [5]. No combination chemotherapy can be defined as clearly superior, but the best results have been obtained with combinations of adriamycin, DTIC, cyclophosphamide and vincristine (CYVADIC) [5].

However, in mixed mesodermal sarcomas of the female genital tract the results are worse [6], indicating that the biology of this tumor type may be different from other adult soft tissue sarcomas. The Gynecologic Oncology Group (GOG) performed a randomized study of adriamycin vs. adriamycin and DTIC in advanced uterine sarcomas and found a response rate of only 15% in 72 patients with mixed mesodermal sarcomas without a significant difference between the two treatment regimens [6]. In a study of the M.D. Anderson Hospital there was a response rate of 16% partial responses in 19 patients with mixed mesodermal sarcomas of the uterus, treated with adriamycin alone or in combination with other chemotherapeutic drugs, and a median survival of only 5.7 months [9]. Treatment with CYVADIC resulted in a response rate of 23% in all patients with sarcomas of the female genital tract, but of only 13% in 16 patients with mixed mesodermal sarcomas accompanied by a median survival of 7 months [7]. In another GOG study chemotherapy with adriamycin at a dose of 75 mg/m^2 for malignant mixed mesodermal sarcomas of the ovary produced one partial response in 10 patients with measurable disease. Of the 21 patients with non-measurable disease 4 remained clinically free of cancer for periods of 2, 17, 21 and 45 months [8].

Cisplatin alone is inactive in adult soft tissue sarcomas [11–13]. However in a report of a phase II trial with cisplatin alone at a dose of 50 mg/m^2 every 3 weeks as second-line chemotherapy for advanced or recurrent measurable mixed mesodermal sarcomas of the uterus, 5 (18%) of 28 patients achieved a response [10]. Clearly there appears to be a reason to study combinations of adriamycin and cisplatin in this tumor type of the female genital tract. In a recent report a response rate of 60% was observed in 15 patients with mixed mesodermal sarcomas of the ovary treated with combination chemotherapy consisting of either cyclophosphamide, adriamycin and cisplatin (CAP) or CYVADIC, with a median survival of 21 months [15].

In our study we observed rapid progression in two patients treated with only adriamycin and cisplatin. In parallel to the treatment of ovarian cancer the next 7 patients were treated with the CHAP-5 regimen. Response was achieved in 5 (83%) of 6 patients with measurable disease, whereas the other patient with measurable disease showed no progression for 5 months. The median survival of the CHAP-5-treated patients was 20 months, with one long-term survivor (67 months). The patient with non-measurable disease had a progression-free survival of 27 months.

In conclusion, this limited pilot study suggests that CHAP-5 combination chemotherapy may be active in mixed mesodermal sarcomas of the female genital tract. The combination should be further investigated in this tumor type.

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