The role of chemotherapy in malignant mixed mullerian tumors of the female genital tract

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Summary

Thirteen patients with malignant mixed mullerian tumor of the female genital tract, treated and followed in our clinic from 1989 to 1999 were retrospectively evaluated. Seven patients (53.8%) with advanced disease or postoperative residual tumor were treated with adjuvant chemotherapy. The median age at diagnosis was 64 years (range: 26-79). All patients underwent primary surgical cytoreduction. Tumors were localized to the endometrium in five (62.5%), to the ovaries in two (25%) and to the fallopian tube in one (12.5%) patient. One patient with endometrial carcinosarcoma had a simultaneous second primary ovarian epithelial carcinoma. Two patients (25%) had a heterologous sarcomatous component. Myometrial involvement included less than half the thickness in one patient, while there was no myometrial invasion encountered in two patients. Five patients (38.5%) had more than 50% of the myometrium invaded. Two patients received additional radiotherapy. Six patients received cisplatinum-based chemotherapy (4 had doxorubicin including combinations), while one patient was treated with a doxorubicin+ifosphamide combination. Five patients (71.4%) had a complete response (CR) to chemotherapy. Response duration in patients with a CR was +13, +67, +10, +14 and +2 months, respectively. After a median follow-up period of 20 months (3-115 months), six patients have died, five are being followed-up with no evidence of disease, one is alive with metastatic disease and one patient is under treatment.

Malignant mixed mullerian tumor of the female genital tract is highly responsive to multimodality treatment strategies. Further prospective studies are required to identify distinct prognostic groups that may benefit from various treatment modalities.

Key words: Malignant mixed mullerian tumor; Gynecologic; Chemotherapy.

Introduction

Malignant mixed mullerian tumors (MMMT) involving the female genital tract are rare tumors that are composed of both malignant epithelial (carcinomatous) and malignant stromal (sarcomatous) elements. The most frequently involved organ is the uterus, followed by the ovaries, fallopian tubes and the vagina in decreasing order of frequency. Also referred to as carcinosarcoma, MMMT account for 1% of all uterine malignancies. This tumor type, which tends to occur in postmenopausal low parity women, is highly aggressive, with early lymphatic and hematogenous spread at initial presentation. Overall survival at two years is reported as 50% for localized involvement, while a lower rate ranging from 15% to 20% is expected for disseminated disease [1, 2].

Surgery is the mainstay of treatment for patients with MMMT. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the standard surgical procedure. Nevertheless, additional cytologic and pathologic samples should be obtained during laparotomy due to a high rate of upstaging, which is reported to range between 12% and 40% [3]. Significant improvement in local control is achieved with radiotherapy, which translates into prolonged survival in patients with stage I and II disease [4, 5].

The role of chemotherapy is not clearly defined. Nevertheless, due to a high incidence of distant metastasis, chemotherapy offers a logical approach for patients with tumors extending beyond the primary site. Single agent studies with cisplatinum and ifosfamide have yielded response rates ranging from 20% to 42%, whereas, doxorubicin appears to show negligable activity in MMMT [3]. Small studies have reported survival rates similar to epithelial carcinomas with platinum-based combinations [6]. Despite high response rates, median overall survival rates range around 18 months [7]. This data confirms the aggressive clinical course of this type of tumor due to a high incidence of early dissemination.

In this retrospective study, we investigated the clinical outcome of our patients with MMMT of the female genital tract, with an emphasis on the potential role of chemotherapy in patients with advanced disease.

Patients and Methods

Thirteen patients with MMMT of the female genital tract were treated and/or followed at our clinic from 1989 to 1999. The median age at diagnosis was 64 years (range: 26-79 years). All patients underwent primary surgical cytoreduction with total abdominal hysterectomy and bilateral salpingo-oophorectomy, which included a thorough exploration of the whole abdominal cavity, with peritoneal washings and swabs from subdiaphragmatic areas and paracolic gutters. Numerous biopsies from the mesentery and omentum and from any suspected nodular lesion or mass were obtained during the operation. Patients with early stage disease received adjuvant radiotherapy at a dose of 50 Gy in 27 fractions. Patients with advanced involvement or residual disease following primary surgery received

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additional chemotherapy and/or radiotherapy, depending on the the primary tumor site and discretion of the treating physician. Following the completion of primary treatment, patients were followed up regularly with 3-monthly intervals for two years; 6-monthly intervals for the next three years and annually thereafter. Follow-up procedures included a thorough physical examination at each visit and radiologic assessment for local relapse or metastatic disease with chest X-rays, pelvic ultrasound imaging or CT-scans at specific intervals.

All statistical data were analyzed by SPSS base 7.5 for Windows (SPSS Inc., Chicago, U.S.A.).

Results

Stage and site of primary tumoral involvement and treatment strategies for all patients are listed in Table 1. Patient no. 7 had a second primary epithelial ovarian tumor diagnosed simultaneously with uterine carcinosarcoma. Of three cases with heterologous sarcomatous components, one was identified as chondrosarcoma and two were unidentified. After a median follow-up period of 20 months (3-115 months), six patients have died, five are being followed-up with no evidence of disease, one is alive with metastatic disease and one patient is under treatment.

Out of seven patients who received chemotherapy, five (71.4%) achieved a complete response. Response duration in those patients was +13, +66.9, +10, +14.3 and +2.4 months, respectively. One patient who received chemotherapy with stage II disease involving the fallopian tubes (no. 6), showed early intraperitoneal dissemination with massive ascites after three cycles. Six patients (85.7%) with stage III disease received adjuvant chemotherapy. One patient refused treatment and died after three months with extensive intraperitoneal disease. Following chemotherapy, two patients with uterine localizations were given additional pelvic radiation. The uterus was the most frequently involved organ (71.4%, five patients), while two patients (28.6%) presented with ovarian involvement. Excluding one patient who was given a combination treatment including doxorubicin and ifosfamide, the remaining five patients received platinum-based combinations. Median response duration for patients who received chemotherapy was 10.0 months (range: 0.73-66.93).

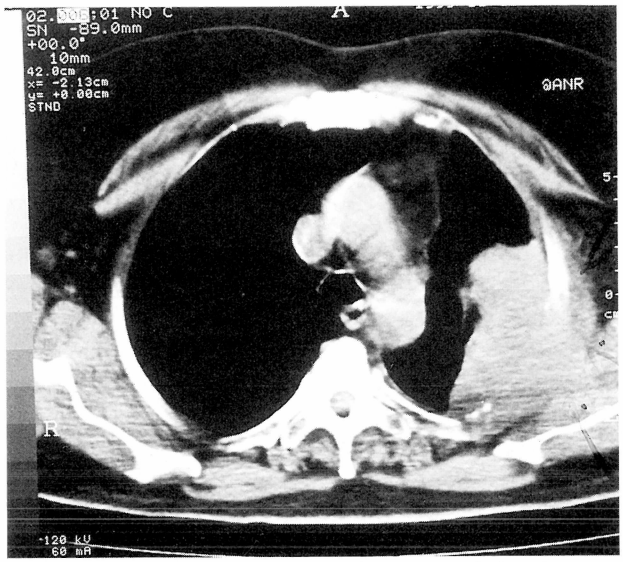

Figure 1. — Thoracix CT-scan showing metastatic involvement before chemotherapy.

Two patients who experienced recurrent disease were treated with second-line chemotherapy. One of them (patient no. 4) was administered a combination of cisplatinum, doxorubicin and cyclophosphamide for six cycles due to a local recurrence of a metastatic lung tumor following metastasectomy (Figure 1). Despite a complete response, which persisted for nine months after the completion of chemotherapy (Figure 2), the patient developed brain metastasis and is currently undergoing radiotherapy. The remaining patient (no. 6), who developed progressive disease with initial chemotherapy, was administered a combination chemotherapy with carboplatinum and paclitaxel and died after three months of progressive disease.

Table 1. — *Disease status and treatment strategies for all patients with gynecologic carcinosarcomas.*

Patient no	Age	Tumor site	Surgery	Stage	Heterol. component	Adjuvant therapy	Type of CT	Response	Response duration (mo)	Site of progression	Therapy for relapse	2nd line CT	Response	Final status	Follow-up period (mo)
1	14	Uterus	Optimal	Ia	Chondro-sarcoma	–	–	CCR	72.7	–	–	–	–	EX	73.0
2	62	Uterus	Optimal	Ib	–	–	–	CCR	50.5	–	–	–	–	NED	50.5
3	56	Uterus	Optimal	Ib	–	RT	–	CCR	8.0	?	–	–	–	EX	10.6
4	53	Uterus	Optimal	Ib	–	RT	–	CCR	87.7	LUNG	Surgery+CT	PA	CR	AWD	115
5	65	Uterus	Optimal	IIa	–	RT	–	CCR	25.0	?	–	–	–	EX	31.6
6	65	F. tube	Optimal	IIc	+ (?)	CT	PAC	PD	0.7	IP	CT	TCa	PD	EX	10
7	26	Uterus	Optimal	IIIa	–	CT	PAC	CCR	13.0	–	–	–	–	NED	16.9
8	79	Uterus	Optimal	IIIa	–	CT	PC	UT	0	–	–	–	–	UT	6.5
9	53	Uterus	Optimal	IIIa	–	CT+RT	AI	CCR	66.9	–	–	–	–	NED	75.0
10	66	Uterus	Suboptimal	IIIa	–	CT+RT	PC	CR	10.0	LIVER	Supportive	–	–	EX	18.8
11	52	Uterus	Optimal	IIIb	–	CT	PAC	CCR	14.3	–	–	–	–	NED	20.6
12	63	Ovary	Optimal	IIIc	+ (?)	CT	PAC	CCR	2.4	–	–	–	–	NED	8.3
13	76	Ovary	Optimal	IIIc	–	–	–	PD	0.8	IP	–	–	–	EX	2.9

(*Abbreviations:* Heterol: heterologous; mo: month; CT: chemotherapy; RT: radiotherapy; F: fallopian; P: cisplatinum; A: Doxorubicin; C: cyclophosphamide; T: paclitaxel; Ca: carboplatinum; CCR: continuous complete response; CR: complete response; PD: progressive disease; IP: intraperitoneal; NED: no evidence of disease; AWD: alive with disease; UT: under treatment; ?: unknown).

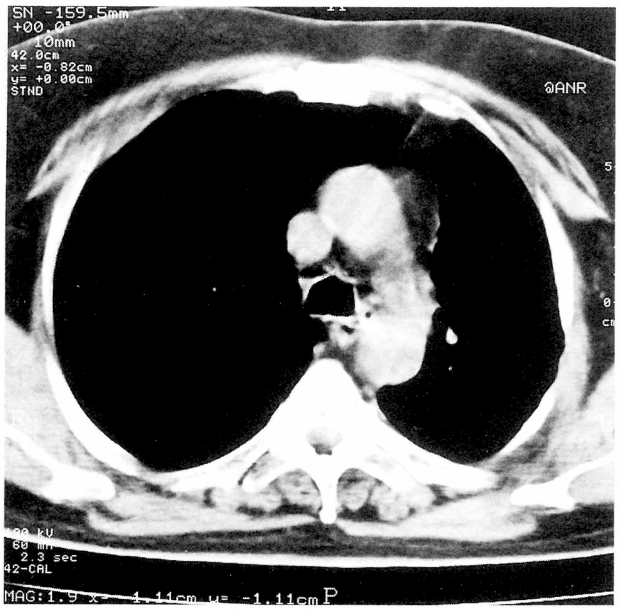

Figure 2. — Regression of the metastatic tumor after 6 cycles of chemotherapy.

Discussion

Although the number of patients are too small to make a valid subgroup analysis, there seems to be a trend towards improved survival in patients with stage I disease compared to those with more advanced involvement. Two patients, including the patient who lived less than one year, have died due to causes not related to their underlying disorder. Despite localized disease at presentation, the two patients with stage II disease had a grave outcome, with one patient dying shortly after progressive intraperitoneal disease unresponsive to chemotherapy. Presence of a heterologous sarcomatous component might be considered as a poor-risk factor contributing to her early death.

Similar to our data, inadequate sample size and heterologous distribution of risk factors preclude making statistical comparisons between various risk groups and treatment strategies. However, stage has been reported as the most important prognostic factor in most series [2, 8]. Median survival in patients with advanced disease has been reported to range between 9.5 and 25 months, with 2-year survival rates estimated as 15-20% in various studies [9-11]. Although there is a trend towards improved survival, our data is not sufficient enough to confirm a survival advantage favoring early stage.

The role of adjuvant radiotherapy in providing local control is controversial. Patients with limited stage at presentation or small residual disease after cytoreduction seem to benefit from irradiation in terms of improved local control [5]. However, incorporation of radiotherapy does not seem to be a logical approach in patients with advanced disease or bulky residual disease following surgical cytoreduction [4].

Chemotherapy may play a relevant role in the management of advanced disease. Cisplatinum and ifosfamide have shown clear-cut activity in patients with MMMT of the female gynecologic tract. Single-agent response rates have been reported as 18-42% with cisplatinum given at 50 mg/m^2 with 3-weekly intervals [12, 13] and as 32% with ifosfamide [14]. Doxorubicin has demonstrated low activity with response rates ranging around 10% [3]. In uterine carcinosarcomas combinations with various agents have not yielded response rates any higher than single agents. Omura *et al.* [15] have reported similar response rates in patients with uterine sarcomas randomized to doxorubicin or doxorubicin and dacarbazine arms, with objective response rates of 16.3% and 24.2%, respectively. A subgroup analysis revealed that heterologous MMMT were more responsive to the combination treatment (27.3 vs 8.7%). Another randomized study by Muss *et al.* [16] showed no survival benefit for the doxorubicin and cyclophosphamide combination compared with single agent doxorubicin in patients with advanced or recurrent sarcomas. Both arms yielded an identical response rate of 19% in patients with measurable disease. A recent randomized GOG study reported a small improvement in response rates (54 vs 36%) and progression-free survival (6 vs 4 months, p = 0.002) with a cisplatinum and ifosfamide combination over ifosfamide alone in advanced carcinosarcoma of the uterus. Due to the lack of a statistically significant survival difference between the treatment arms and substantial toxicity in the combination arm with six treatment-related deaths, the investigators have concluded that this combination might not be considered as a beneficial therapeutic option in this subset of patients [17]. Although, these randomized studies have failed to show a significant survival advantage favoring combinations, most institutions have preferred multi-agent treatment schedules based on high response rates attained in several phase II studies. Plaxe *et al.* [18] reported an 85% objective response in their series of 13 patients with advanced disease given cisplatinum and doxorubicine with or without cyclophosphamide. The median progression-free interval in patients who achieved a complete response was reported as 17 months [18]. In our group, patients with uterine involvement and a complete response to chemotherapy following optimal cytoreduction are still alive after a disease-free interval of 17 months (17-75 months), which is comparable to the reported data. Excluding one patient with ovarian carcinosarcoma who has recently completed the planned treatment schedule, the two patients with advanced ovarian and fallopian tube involvement displayed a highly aggressive course that resulted in death after three and ten months, respectively. Limited data exists regarding the management of ovarian MMMT, and is mostly based on small-sized retrospective evaluations. All these studies have confirmed the highly malignant behavior of this tumor type, emphasizing the high ratio of patients presenting with advanced disease, which is not amenable to curative resection. Muntz *et al.* [10] observed median overall survival intervals ranging from 10 to 24 months, depending on optimal cytoreductability. They concluded that optimal cytoreduction followed by chemotherapy

was associated with a longer progression-free survival, however other series have conflicting data [9, 18]. Despite the lack of randomized studies to justify a beneficial role favoring combinations compared to single-agent schedules, combination regimens are preferred by many institutions. A variety of combinations including cisplatinum, doxorubicin, dacarbazine and ifosfamide have yielded response rates ranging from 27 to 100% and median survival rates around 16 and 18 months [19-21]. Sit *et al.* [22] in their recent report share their experience with two combinations in patients with advanced ovarian MMMT. They observed a median survival of 23 months and significant toxicity with a cisplatinum and ifosfamide combination. The second regimen consisting of carboplatinum and paclitaxel, yielded a median survival of 19 months with a substantial reduction in toxicity and hospitalization costs compared to the former combination.

Unfortunately, we are not able to draw definite conclusions regarding the influence of various prognostic factors or treatment strategies in MMMT of the female gynecologic tract in this study due to the limitations of the small sample size. Nevertheless, we can conclude that the presence of an epithelial component provides a strong rationale favoring the potential role of adjuvant chemotherapy in advanced disease. In addition to vigorous surgical measures, novel therapeutic approaches are needed to improve the grave outcome in this group of patients who are unresponsive to current treatment strategies.

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