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Cisplatin, doxorubicin and ifosfamide in carcinosarcoma of the female genital tract. A phase II study of the European Organization for Research and Treatment of Cancer Gynaecological Cancer Group (EORTC 55923)

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Abstract

Carcinosarcomas of the female genital tract are highly malignant tumours composed of carcinomatous and sarcomatous elements. In the past, these tumours were frequently treated as sarcomas. However, a number of arguments, including the sensitivity of these tumours to platinum-based chemotherapy, suggest that these tumours behave more like poorly differentiated carcinomas. The European Organization for Research and Treatment of Cancer (EORTC) Gynaecological Cancer Group therefore decided to perform a prospective phase II study in patients with advanced or metastatic carcinosarcoma with an approach such as that used in gynaecological carcinomas. Eligible patients could have primary or recurrent disease, but prior radiotherapy or chemotherapy was not allowed. The treatment plan recommended upfront debulking, followed by chemotherapy with cisplatin, ifosfamide and doxorubicin. Patients who could be debulked to non-measurable disease remained eligible for the study, but the response assessment was restricted to patients who had measurable disease before the start of chemotherapy. A total of 48 patients (39 primary disease, 9 recurrent disease) were registered, 41 of them being eligible. In 9 patients, all macroscopic lesions could be removed, 32 patients were left with residual disease and were assessable for response. The overall response rate was 56%: a complete response (CR) was observed in 11 (34%) patients and partial response (PR) in 7 (22%) patients. No change occurred in 5 patients and progression in 2 patients. In 7 patients, response could not be assessed. Median survival for all of the 41 eligible patients was 26 months. Severe leucopenia and thrombocytopenia were common and necessitated dose reductions or delays in 60% of patients. From a clinical point of view, the most severe non-haematological toxicity was renal dysfunction, and one patient died of this

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complication in the absence of disease progression. The results of this study are in-line with the hypothesis that carcinosarcomas are chemosensitive, in particular for the currently investigated regimen. The treatment also included upfront cytoreduction when feasible. Considering the observed toxicities, alternative platinum-based regimens with more favourable toxicity profiles should be explored.

Keywords: Carcinosarcoma; Cisplatin; Doxorubicin; Gynaecological cancer; Ifosfamide; Phase II

1. Introduction

Carcinosarcomas (CS) of the female genital tract, also known as malignant mixed mesodermal tumours, constitute a group of infrequently occurring malignant neoplasms consisting of proliferating epithelial and mesenchymal elements. They usually arise in the uterus or the ovary, but sporadic cases of CS arising outside these organs have been reported [1–3].

Patients with CS have a poor prognosis, with 2-year survival rates of 53% for CS confined to the uterus and 18–27% for those with extension beyond the uterus [5–6]. Survival data for CS of the ovary appear comparable to those reported for advanced uterine CS's, as the majority of patients with ovarian CS present with stage III-IV disease [7–9]. In one report only 3 out of 13 patients with CS of the ovary diagnosed between 1973 and 1984 survived for more than 1 year [10], although more recent studies report median survival times for ovarian CS varying between 11 and 18 months [11–14].

There has been much debate about the histogenesis of these tumours [8]. The discussion focuses on the question of whether these tumours represent truly composite tumours of malignant mesenchymal and epithelial ancestor cells, or arise from a common (epithelial) stem cell. With respect to this, opinion has been expressed that these tumours most likely originate from the multipotential cell of coelomic epithelium [8]. The question regarding the histogenesis of CS obviously has clinical relevance, as the chemotherapeutic approach to sarcomas differs from that used in carcinomas, especially with regard to the use of platinum-containing regimens. Based on the presence of sarcomatous elements, patients with CS have frequently been included in series of soft tissue sarcomas. However, the correctness of this approach might be challenged considering data regarding the histogenesis of these tumours. Immunohistochemical investigations using staining of intermediate filaments with markers of epithelium, mesenchyme and skeletal muscle revealed an extensive overlap with regard to the expression of these markers between uterine CS and poorly differentiated uterine carcinoma [15,16]. Some authors therefore concluded that CS represents a heterogenous group of tumours, including both carcinomas as well as true carcinosarcomas [15]. Others have stated that these tumours are most probably part of a spectrum of carcinomas [17], or at least behave like carcinomas [16,18,19]. Additional argument to treat these tumours like carcinomas is supplied by the observation that metastases of CS are frequently composed of only the carcinomatous component. Consequently, this may imply that these tumours are not a separate entity, but in fact represent metaplastic carcinomas [17,18].

Based on these considerations, the EORTC Gynaecological Cancer Group (GCG) decided to treat these patients like epithelial neoplasms, and, consequently, to explore a platinum-based regimen. Ifosfamide was included instead of cyclophosphamide because of its documented activity in CS [20,21], and doxorubicin since data suggest that it is an active drug in this disease when administered in combination with cisplatin [11,22,23].

2. Patients and methods

Patients defined by member institutions of the EORTC GCG to have CS of the female genital tract were eligible to be entered. Eligibility criteria included advanced or recurrent CS of the ovary, fallopian tube or the uterus and, in case of recurrent disease, documented progression was required. Previous chemotherapy or radiotherapy was not allowed. The upper age limit was set at 75 years. World Health Organization (WHO) performance status had to be 0–2, with a life-expectancy >2 months. Grossly normal organ functions were required, defined as white blood cells $>4.0\times10^9$/l, platelets $>100\times10^9$/l, serum creatinine <120 μmol/l or creatinine clearance >60 ml/min, serum bilirubin <25 μmol/l and normal cardiac function. Assessment of left ventricular ejection fraction either by echocardiography or by scintigraphy was recommended in cases of doubt. All patients had to give informed consent.

A staging laparotomy with an attempt at debulking was recommended for all patients with disease confined to the abdominal cavity. Patients who were successfully debulked to non-measurable lesions remained eligible to enter the study. The chemotherapy had to start within 6 weeks from surgery. Prehydration consisted of 1000 ml 0.9% normal saline over 3 hours. During the prehydration, doxorubicin 45 mg/m^2 was administered by intravenous (i.v.) injection over 5 min, approximately 30 min before the administration of cisplatin. Cisplatin 50 mg/m^2 in 500 ml 0.9% saline was administered over 3 h, followed by ifosfamide 5 g/m^2 dissolved in 4000 ml 0.9% saline over 24 h. The total dose of mesna was 5 g/m^2, 25% of the total dose administered as an i.v. bolus

immediately preceding the commencement of the ifosfamide infusion, 50% administered concurrently with the ifosfamide infusion, and 25% of the dose administered over 12 h dissolved in 2000 ml 0.9% saline following the ifosfamide infusion. Complete blood counts consisting of Hb, Ht (haematocrit), white blood cells (WBC) + differential, and platelets had to be performed each week while on treatment. Chemotherapy was scheduled every 21 days for six cycles.

Dose reductions were foreseen for haematological and non-haematological toxicities, as assessed during and at the end of each cycle, using WHO toxicity criteria. When on day 21 the absolute neutrophil count (ANC) was $<2.0\times10^9$/l or the platelet count $<100\times10^9$/l treatment had to be postponed for 1 week, up to a maximum of 3 weeks. In these circumstances, or when the WBC nadir was $<1.0\times10^9$/l or the ANC nadir $<0.5\times10^9$/l for a period of more than 7 days, administration of granulocyte-colony stimulating factor (G-CSF) was allowed. Otherwise, or when the WBC nadir was $<1.0\times10^9$/l or the ANC nadir $<0.5\times10^9$/l for a period longer than 7 days, despite the use of G-CSF, the dose of doxorubicin and ifosfamide had to be reduced by 20% in the next cycle. In addition, when the platelet nadir was $<50\times10^9$/l, the dose of doxorubicin and ifosfamide had to be reduced by 20% in the next cycle.

The dose of doxorubicin was reduced by 10 mg/m^2 in cases of WHO Grades 3-4 stomatitis or diarrhoea. When on day 21 creatinine clearance had decreased below 40 ml/min, or serum creatinine increased to values above 150 μmol/l, the administration of the next cycle was delayed for a maximum of 3 weeks. When renal dysfunction had not recovered by that time, the patient went off the study. Cisplatin was withdrawn from the schedule in cases of neurotoxicity grade >2 or clinical hearing loss. In such circumstances, treatment was continued with doxorubicin and ifosfamide. In cases of encephalopathy, ifosfamide was withdrawn from the schedule. Chemotherapy was stopped in cases of clinical signs of cardiac toxicity (congestive heart failure). Response evaluation was performed after three cycles and at the end of chemotherapy. Standard WHO reponse criteria were used. A clinical complete response (CR) was defined as the disappearance of all clinically measurable and evaluable disease, and a partial response (PR) as a reduction of all measurable lesions of more than 50%, for a duration of at least 4 weeks. When measurable lesions increased less then 25% or decreased less than 50% for a duration of at least 6 weeks, this was called stable disease. Progressive disease was defined as an increase of measurable lesions of more than 25% or the occurrence of new lesions. Early death was defined as death during the first 6 weeks after commencement of chemotherapy without severe toxicity, and a toxic death any death to which drug toxicity was thought to have had a major contribution. After completion of chemotherapy, a second-look laparotomy was left to the discretion of the investigator. The toxicity analysis was based on all patients who received at least one dose of the cisplatin, doxorubicin and ifosfamide combination. Response analysis was confined to eligible patients with residual disease and survival analysis to eligible patients only. The duration of response (responders only) was calculated from the commencement of treatment until the documentation of progression. Survival was dated from the start of treatment until death or the date of last visit. Time to event was estimated using the Kaplan–Meier technique.

3. Results

Between October 1993 and April 1998, a total of 48 patients from seven countries were registered. Out of these, 7 patients were ineligible. One patient was ineligible because of prior radiotherapy, 1 patient because of inappropriate disease stage (International Federation of Gynecology and Obstetrics (FIGO) stage 1) and 5 patients because of the wrong histology, (two leiomyosarcoma, two endometrial stromal sarcoma and one undifferentiated adenocarcinoma). Table 1 summarises the patient's characteristics. 37 patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, 2 patients had another surgical procedure, 6 patients had a biopsy only before starting chemotherapy, and in 3 patients information with regard to the surgical procedure was not available. In 9 patients, all macroscopic lesions could be removed,

Table 1
Patient characteristics

Total number of patients enrolled	48
Ineligible	7
Total number of eligible patients	41
Median age in years (range)	61 (37–74)
Menopausal status	
Pre-/postmenopausal	2/46
Performance status 0/1/2	24/19/5
Primary/recurrent disease	39/9
Residual disease after surgery	
No/yes	9/39 (of whom 32 eligible)
Measurable disease	36 (of whom 29 eligible)
Original site of tumour	
Uterus	22
Fallopian tube	3
Ovary	20
Other	2
Unknown	1
Cell type	
Homologous	21
Heterologous	24
Unknown	3
FIGO stage	
I/II/III/IV/unknown	7/8/26/6/1

FIGO, International Federation of Gynecology and Obstetrics.

whereas 32 eligible patients were left with residual disease, and were available for the assessment of response.

In these 32 patients, a CR was observed in 11 (34%) patients and a PR in 7 (22%) patients, accounting for an overall response rate (CR + PR) of 56% (95% Confidence Interval (CI): 39–73%). No change occurred in 5 patients, disease progression in 2 patients, whereas in 7 patients the response was not assessable, one of them being an early death. Median duration of the response (CR/PR responders only, 18 patients) was 34 months (range 5–48 months). Median progression-free survival was 11.9 months for patients with residual disease, and 25.2 months for patients without residuals (Fig. 1a).

At the time of analysis 22 of the 41 eligible patients had died (54%), 19 of which (86%) were due to malignant disease, 1 (5%) due to the toxicity of treatment, 1 (5%) of an associated chronic disease and 1 (5%) because of an inter-current disease. Median survival was 26 months for all 41 eligible patients (21 months for the 32 patients with residual disease, and 53 months for the 9 patients without residual disease (non significant) and the estimated 3-year survival was 43% (95% CI: 26–61%) (Fig. 1b). Median survival was 22 months for the 35 eligible patients with primary disease at entry into the study.

For 40 out of 41 eligible patients, the actual number of chemotherapy cycles delivered was available. 25 patients (61%) completed six cycles. The number of patients who had received 1, 2, 3, 4 and 5 cycles only was 3, 2, 3, 4 and 3, respectively. Table 2 summarises the worst haematological toxicity for all cycles for all of the patients with data and for eligible patients only. Table 3 lists the non-haematological toxicity. As expected, severe leucopenia and thrombocytopenia were common and necessitated dose reductions/delays in 60% of patients. G-CSF was used in 69 cycles. Relative dose intensity (actual/planned *100, mg/m^2/wk) was 85% for doxorubicin, 89% for cisplatin, and 86% for ifosfamide. Table 3 lists the non-haematological toxicity. From a clinical point of view the most severe non-haematological toxicity was renal dysfunction. 3 patients had to stop treatment because of this complication. One patient ultimately died of severe renal failure (in the absence of disease progression) after the first cycle.

Table 2
Haematological toxicity

	All patients with data (%) ($n=42$)		Eligible patients with data (%) ($n=37$)	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Haemoglobin	47.7	45.2	48.6	43.2
WBC	4.8	92.9	2.7	94.6
Granulocytes	10.6	81.6	9.1	84.8
Platelets	16.7	61.9	16.2	64.8

WBC, white blood cells.

4. Discussion

Carcinosarcoma is associated with a poor prognosis, especially in the presence of advanced disease. While there exists no official staging system for CS, usually the FIGO staging classification for carcinomas of the uterus and ovary, respectively, is used. Many studies have indicated the importance of tumour stage using the FIGO classification with regard to the prognosis of CS [6,7,9,24–27]. Patients with stage I-II disease have 5-year survival rates of 20–35%, whereas patients presenting with a more advanced disease will usually have died by that time [6,8,9,28]. Age, menopausal status and performance status are also associated with prognosis [4]. Several studies have reported that patients with homologous CS may have a better prognosis than those with heterologous CS [27,29,30], but, in general, this distinction has not been considered to be an important prognosticator [4,7,8,24].

There is no universally accepted standard as to how CS should be managed. This applies to the role of surgical debulking, radiotherapy and the choice of chemotherapeutic agents. The lack of consensus is understandable due to the presence of both carcinomatous and sarcomatous malignant elements in the tumour specimens. Moreover, due to the rarity of the tumour, guidance from results of randomised trials is not available. Based upon the superior responsiveness of CS to platinum-based combination therapy (reviewed in [23], supported by [30]), and supported by the hypothesis that the sarcomatous elements in this tumour type might represent metachronous carcinoma [17,18], the EORTC GCG embarked on a proposal to treat patients with CS like poorly differentiated adenocarcinomas. Upfront surgical debulking followed by platinum-based chemotherapy were considered key elements to this approach.

Complete surgical resection of the tumour most likely provides the best outlook for long-term survival. An accurate staging laparotomy with abdominal hysterectomy, bilateral adnexectomy and resection of as much

Table 3
Non-haematological toxicity

	All patients with data (%) ($n=44$)		Eligible patients with data (%) ($n=39$)	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Nausea/vomiting	43.2	52.3	46.1	48.7
Diarrhoea	18.2	4.6	15.3	5.1
Oral	27.3	9.1	25.6	10.3
Renal toxicity	9.3	9.3	10.5	7.9
Cardiotoxicity	11.4	4.6	10.2	5.1
Fever	34.1	4.6	35.8	5.1
Haemorrhage	6.8	4.6	5.1	5.1
Alopecia	27.3	61.4	25.6	64.1
Neurotoxicity	29.5	18.2	20.5	15.4

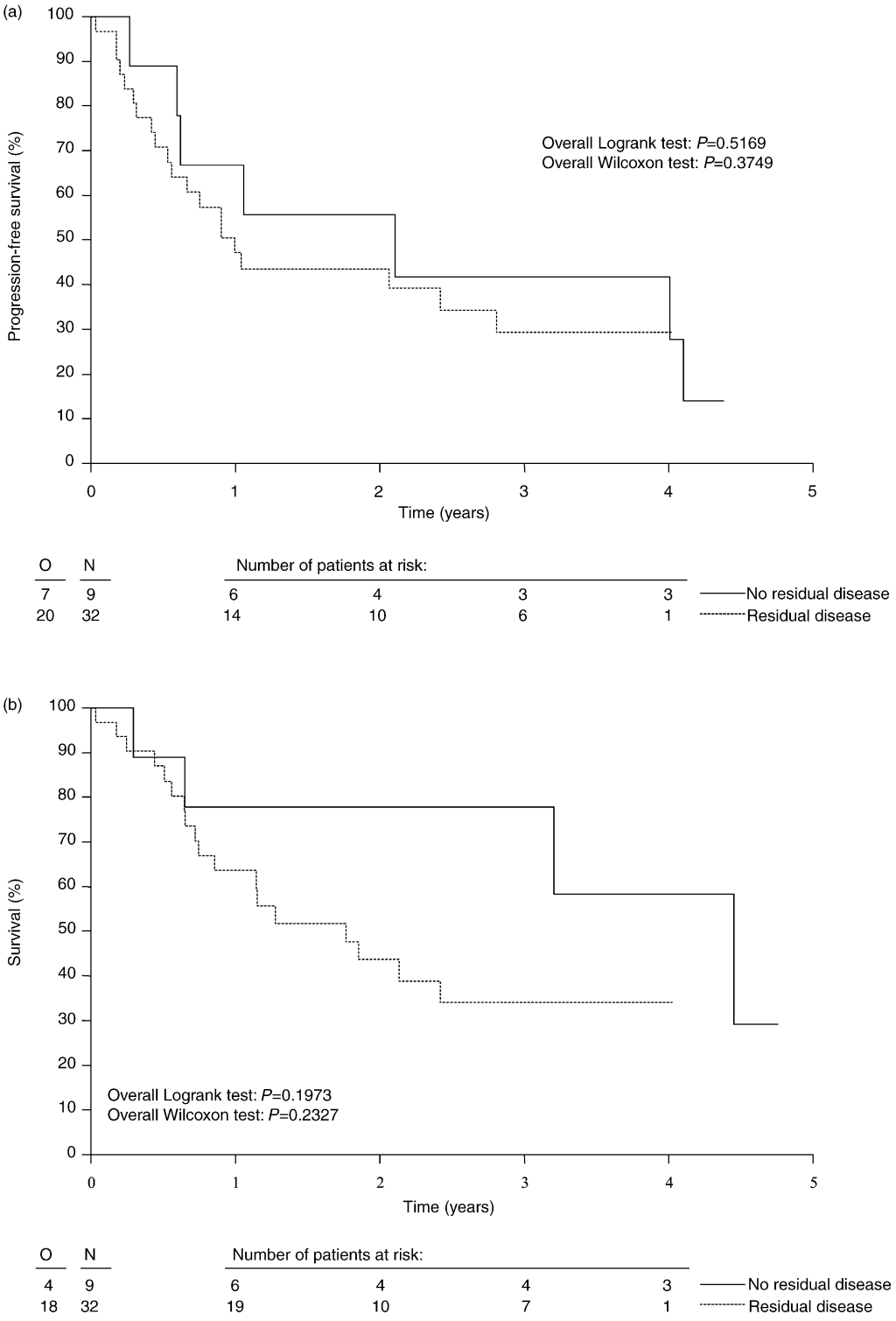

Fig. 1. Progression-free survival and overall survival of patients with carcinosarcoma treated with cisplatin, doxorubicin and ifosfamide, according to residual disease status. (a) Progression free survival time. (b) Survival time.

tumour as possible is therefore considered as the optimal approach to patients with CS [6,24,31]. However, localised CS treated by surgery alone carries a high risk of local recurrence and metastatic disease. Radiotherapy to the pelvis may reduce the risk of local recurrences, but has no major impact on survival [5,6,12,32,33]. Adjuvant chemotherapy with doxorubicin in patients with stage I-II disease did not improve survival [34], but a retrospective study reported an improved survival in 6 patients treated with

vincristine, actinomycin D and cyclophosphamide compared with 23 patients receiving no chemotherapy [23]. More convincing were the results obtained with a cisplatin-based chemotherapy regimen, as only four recurrences were observed in a group of 17 poor risk patients with limited disease after a median follow-up of 34 months [22]. A similar figure was observed in an analysis of 38 patients with stage I and II CS of the uterus [35]. In the subgroup of 21 patients, who were treated with platinum-based chemotherapy and radiotherapy after thorough surgical staging and tumour resection, only two recurrences were observed after a mean follow-up period of 59 months. In addition, patients with more advanced stages seem to benefit from an optimal tumour reduction. Due to confounding factors, such as the extent of the disease and small numbers of patients, it is difficult to prove that surgical debulking is an essential element in the treatment of CS. In the present study, the median survival of patients who could be optimally debulked did not differ significantly from that of patients with residual disease, but we consider our results in-line with other studies that also suggest a benefit from optimal cytoreduction [14,30].

Cure may not be possible in the majority of patients left with suboptimal disease, but the results of the present trial show that platinum-based combination chemotherapy can produce meaningful responses in approximately 55% of patients within a multicentre setting. In this respect, the aim of the study, namely to prove that a treatment directed at the malignant epithelial component of carcinosarcoma would be critical for obtaining tumour control, has been achieved. The results from this trial, as well as those reported by others [11,37,38], show that cytoreduction and platinum-based regimens are the cornerstone of treatment for carcinosarcoma. Whether the cisplatin, ifosfamide and doxorubicin schedule such as that used in this study is optimal can nowadays be questioned, as novel agents with activity in ovarian and endometrial cancers have entered the clinic. The regimen appeared cumbersome in an older patient population and the nephrotoxicity and myelosuppression, in particular, were of concern. This toxicity has also been observed in other studies [36,38]. Most probably, these tumours can be treated in the same way as poorly differentiated uterine and ovarian malignancies [23,37]. This suggests that a platinum plus paclitaxel combination could be a reasonable alternative [38]. For this reason, the next trial of the EORTC Gynaecological Cancer Group in carcinosarcoma will be based upon such a combination.

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