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A Randomised Study of Cisplatin Versus Thiotepa as Induction Chemotherapy in Advanced Ovarian Carcinoma

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Between 1980 and 1984, a total of 171 patients with advanced epithelial ovarian carcinoma and residual tumour after surgery were randomly assigned to treatment groups receiving either cisplatin or thiotepa. The objective of the study was to evaluate the regimes with regard to response and survival. The two groups were well balanced with respect to age, FIGO stage, histology, grade and residual tumour after surgery. In the cisplatin group, 66% responsed to treatment compared to 38% in the thiotepa group ($P < 0.00005$). The median progression-free survival was 10.5 months and 6.3 months, respectively. The corrected survival was somewhat, but non-significantly, higher in the cisplatin group than in the thiotepa group, with an 8-year corrected survival of 10.6 and 7.4%, respectively. In a multivariate analysis, based on progression-free survival with FIGO stage, residual tumour after surgery, histological type and grade as covariables, treatment with thiotepa had a relative risk of 1.64 compared to cisplatin (95% confidence interval 1.17–2.30, $P = 0.004$).

Key words: ovarian cancer, cisplatin, thiotepa
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INTRODUCTION

SINCE CISPLATIN was introduced as single-agent treatment in patients with advanced epithelial ovarian cancer, several studies [1] have demonstrated improved survival using this drug. Later, there were high expectations for combination chemotherapy, that is cisplatin with doxorubicin, hexamethylmelamine, cyclophosphamide and various other cytostatics, but results on prolonged long-term survival were disappointing [2–4]. Some have argued that single-agent cisplatin is as effective as platinum-based combinations when it comes to overall survival, and the

Table 1. Patients' characteristics

	Cisplatin group	Thiotepa group
No. of patients	85	86
FIGO stage		
2B	3	3
3A	1	0
3B	8	15
3C	49	45
4	24	23
Size of residual disease		
< 2 cm	21	22
2–5 cm	35	36
> 5 cm	29	28
Histological type		
Serous	47	62
Mucinous	11	4
Endometrioid	13	3
Clear cell	3	7
Mixed	0	1
Unclassified	11	9
Tumour grade		
1	11	6
2	20	21
3	51	52
Unknown	3	7

quality of life is better, with less toxicity and less discomfort [5]. However, a recent meta-analysis of trials over two decades in advanced ovarian cancer came to the conclusion that cisplatin-based combination therapy is more effective [6]. When carboplatin came into use, it was soon considered a better alternative to cisplatin because the side-effects were more acceptable although there is a tendency to bone marrow depression which may cause dose reductions, rendering the treatment less effective.

Thiotepa, the alkylating agent triethylene-thiophosphoramide, has been in use since the 1950s for ovarian cancer. Like cisplatin, it induces DNA damage and inhibits repair of DNA damage [7]. Studies in the early 1970s showed objective remissions associated with improved survival [8, 9]. The acute side-effects are mild, with an acceptable short duration of myelosuppression, although the risk of secondary leukaemia seems present after long-term use [10]. However, single-drug or combination therapy with this alkylating agent now seems left to second-line treatment and therapy on special indications, such as old age and reduced performance status. The objective of this study was to evaluate the regimes of cisplatin versus thiotepa as single-drug treatment in advanced ovarian carcinoma after cytoreductive surgery, with regard to response and survival.

PATIENTS AND METHODS

Between 1980 and 1984, a prospective, randomised study was performed, recruiting 171 patients with advanced ovarian cancer. Eligible for the study were patients with epithelial ovarian carcinoma with residual tumour after surgery. Patients with borderline ovarian tumours were not included.

All histological slides were reviewed in the Department of Pathology at our hospital. Histological classification was based on criteria defined by the WHO [11]. Clear cell carcinomas were not graded.

Clinical staging was based on the primary operative report, and was performed according to the systems adopted by the International Federation of Gynaecology and Obstetrics (FIGO) [12]. All patients underwent primary surgery, in 133 cases at local hospitals and in 38 cases at our department. Standard surgical procedures were total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy. In case surgical debulking was deemed impossible, the surgical procedure was reduced to an explorative laparotomy with biopsies. Induction chemotherapy was initiated at our department 2–4 weeks after surgery. The patients were randomly allocated to either cisplatin 75 mg/m^2 every 28 days for six courses or thiotepa 60 mg intramuscularly (i.m.) as loading dose, followed by 30 mg i.m. every 14 days for 10 courses. 85 patients were treated with cisplatin and 86 with thiotepa. The distribution of patients according to FIGO stage, residual tumour after surgery, histological type and grade is shown in Table 1.

Objective response to treatment was evaluated clinically or radiologically. Complete response was defined as complete disappearance of all clinically detectable tumour(s) for at least 4 weeks. Partial response was defined as a 50% or more decrease in total size of measurable disease determined by two observations not less than 4 weeks apart (compared with status before first course). Stable disease was defined as less than a 50% reduction or less than a 25% increase of measurable disease for a

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Table 2. Distribution of patients to second-line therapy

	Second-line therapy					
	Thiotepa	Cisplatin	Carboplatin	Abdominal radiotherapy	Other	Total
Cisplatin group	15	0	11	14	16	56
Thiotepa group	0	40	3	3	6	52

duration of at least 12 weeks. Progressive disease was defined as more than a 25% increase of any parameter or new lesions or new effusions. Non-evaluable disease was defined as disease undetectable by clinical or radiological examination.

Six months after randomisation and start of induction chemotherapy, a second-look operation was performed in 50 patients, 33 in the cisplatin group, and 17 in the thiotepa group. Second-line treatment was given as outlined in Table 2.

Patients were followed-up by routine gynaecological examination at the Norwegian Radium Hospital or at local hospitals, at intervals of 3 months during the first year, 6 months during the second year and then once yearly. All patients were followed until death or to December 1992. Follow-up information was collected from the medical records and from the Cancer Registry of Norway.

Differences between the groups were evaluated by the χ^2 or the Fisher test, as appropriate. Survival was calculated from the time of diagnosis using the method of Kaplan and Meier. Observed differences in survival were examined by the log rank test. Cox multiple regression analysis was used for multivariate analysis. All P values are two sided. A significance level of 0.05 was used. Survival rates were based on death attributed to ovarian cancer only.

RESULTS

85 patients were allocated to treatment with cisplatin and 86 to treatment with thiotepa. Pertinent clinical and histopathological variables for patients in the two treatment groups are shown in Table 1. There were no differences in distribution with regard to FIGO stage, size of residual tumour after surgery, histological type or tumour grade between the two groups. An exploratory laparotomy with biopsies was performed in 34 patients, 13 stage IIIC and 3 stage IV patients in the cisplatin group, and 12 stage IIIC and 6 stage IV patients in the thiotepa group. The rest underwent tumour reductive surgery. Median age was 57 years in both groups (range 23–75). All patients were followed until death or December 1992, with a median follow-up for survivors of 110 months (range 100–153).

In the cisplatin group, 17 showed a complete response, 34 a partial response, 18 had stable disease, 8 had progressive disease and 8 had non-evaluable tumours. In the thiotepa group, 11 showed a complete response, 20 a partial response, 28 had stable disease, 22 had progressive disease and 5 had non-evaluable tumours. Based on patients with evaluable tumours, the response rate was 66.2% in the cisplatin group and 38.3% in the thiotepa group ($P < 0.00005$). The complete response rate was 22.1% in the cisplatin group and 13.6% in the thiotepa group ($P = 0.23$).

Second-look surgery was performed in 50 patients who had completed induction chemotherapy and were considered to have clinical complete or partial response, or stable disease, that is, 33 patients in the cisplatin group and 17 in the thiotepa group. Cytoreductive surgery was performed in 8 patients in the cisplatin group and in 3 patients in the thiotepa group. In 6 cases in the cisplatin group all residual tumour was removed, in the remaining cases, a cytoreduction to residual tumour of less than 2 cm was performed.

Second-line treatment was given to 108 patients as outlined in Table 2. A crossover to treatment with thiotepa was carried out in 15 cases in the cisplatin group, and to treatment with cisplatin in 43 cases in the thiotepa group. Of 15 patients in the cisplatin group given thiotepa as second-line treatment, 2 showed a partial response (13.3%), none showed response to treatment with carboplatin, and 3 had a complete and 1 had a partial response to whole abdominal irradiation. In the thiotepa group, of the 43 patients who received second-line treatment with cisplatin or carboplatin, 6 had a complete and 7 had a partial response, giving a response rate of 30.2%. All 3 patients given abdominal radiotherapy responded.

Patients in the cisplatin group showed significantly longer progression-free survival than patients in the thiotepa group (log rank, $P = 0.025$; Figure 1), the median progression-free survival was 10.5 months in the cisplatin group and 6.3 months in the thiotepa group. The corrected survival was somewhat higher in the cisplatin group than in the thiotepa group, but the difference was not statistically significant ($P = 0.155$; Figure 2). The median corrected survival was 20 and 14 months, respectively. The 8-year corrected survival was 10.6 and 7.4% in the cisplatin and thiotepa groups, respectively.

By Cox multivariate analysis, based on progression-free survival and including FIGO stage, residual tumour after surgery, histological type and grade as covariables, the treatment group was the strongest independent prognostic factor with a relative hazard of 1.64 (95% confidence interval 1.17–2.30, $P = 0.004$) for thiotepa treatment compared to cisplatin.

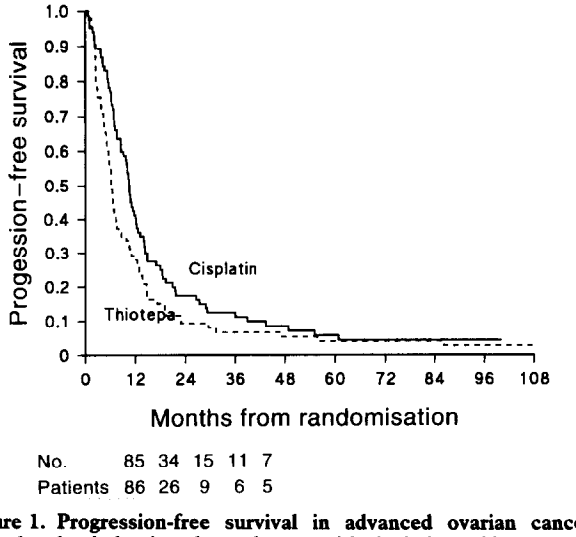

Figure 1. Progression-free survival in advanced ovarian cancer related to induction chemotherapy with cisplatin or thiotepa.

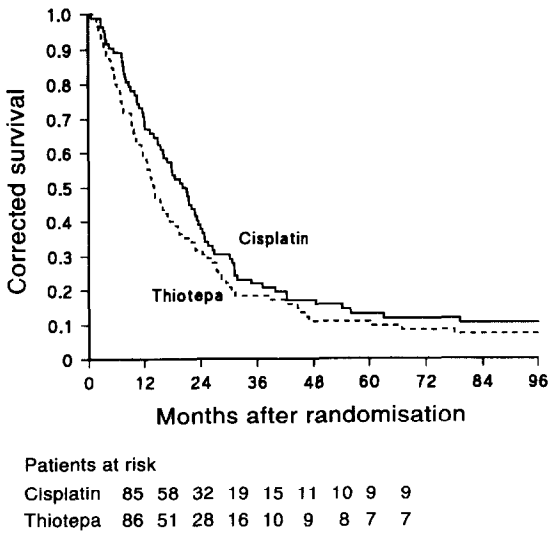

Figure 2. Corrected survival in advanced ovarian cancer related to induction chemotherapy with cisplatin or thiotepa.

Problems of toxicity were minor. In the cisplatin group, 1 patient changed treatment because of general weakness and dizziness and some patients complained of neurotoxicity of sensory type, but this was not so severe as to stop or change therapy.

In total, 5 patients died of intercurrent diseases, 1 of sepsis and 4 of lung emboli. 3 patients died of complications, 1 of postoperative infection, 1 of toxic enteritis after abdominal radiotherapy and 1, in the thiotepa group, died of liver failure after second-line carboplatin.

DISCUSSION

Surgery is considered the mainstay in diagnosis and treatment of ovarian carcinoma [13, 14]. In advanced disease, the need of postoperative chemotherapy is obvious and high response rates have been obtained, although long-term survival has been poor. This study was performed during 1980–1984 when single-agent treatment was still commonly used. Today, combination chemotherapy is mostly used except in older patients or in patients with low performance status. For these patients, the choice of treatment is often a platinum compound or an alkylating agent. Our study has a complete follow-up and an observation time for survivors of at least 8 years. Most of the patients were in an advanced stage and all had residual tumour after surgery. The study was well balanced with no marked differences between the two groups with respect to pertinent clinical and histopathological variables.

The overall response rate was clearly better with cisplatin treatment although the difference in the rate of complete clinical response was smaller and was not statistically significant. The response rate obtained in the cisplatin group is somewhat higher than those obtained with cisplatin single-drug treatment in other studies [3], but our results are similar to response and survival rates from cisplatin combination therapy [15].

A response rate of 30% for thiotepa is reported in the literature [16] and in a study from 1970 [8], on 144 patients treated with thiotepa, 25% of the patients died within 9 months, 50% shortly after 1 year and the 5-year survival was less than 10%. This is similar to our results.

The progression-free survival was significantly higher in the cisplatin group than in the thiotepa group. The difference in corrected survival was somewhat smaller and statistically non-significant. The cross-over to second-line treatment with a platinum compound in half of the patients in the thiotepa group probably rescued patients in that group, as 30% of these patients showed response to that treatment, and thereby reduced the difference in corrected survival between the two groups. It is noteworthy that the survival for the thiotepa group remained lower than for the cisplatin group in spite of the crossover to second-line treatment with either cisplatin or carboplatin. In the cisplatin group, the response to second-line treatment was poor. This is in agreement with other studies [17, 18] showing a low response rate to alkylating agents in cisplatin-resistant ovarian tumours. Secondary cytoreduction at the time of second-look was performed in 9.4% of patients in the cisplatin group and in 3.5% in the thiotepa group. It is unlikely that this influenced the difference in corrected survival between the two groups.

The difference in long-term survival between the two groups was 3%. The 8-year survival was only 10.6% in the cisplatin and 7.4% in the thiotepa group, respectively. These low figures might be explained by the relatively high number of patients with FIGO stage IIIC and IV. Our results show that treatment with cisplatin gives higher response rates and higher progression-free survival rates than treatment with thiotepa in single-agent treatment. A meta-analysis [6] found cisplatin and carboplatin almost equally effective, and as carboplatin is better tolerated with markedly less emesis, renal dysfunction and neuro- and ototoxicity, it is to be considered as an alternative to cisplatin in single-agent treatment. From a cost–benefit point of view, it is interesting that thiotepa might be a useful alternative to platinum treatment where competent hospital treatment is scarce.

In conclusion, cisplatin was found to be superior to thiotepa in single-agent treatment of advanced ovarian cancer.

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Cisplatin and Etoposide Versus Cyclophosphamide, Epirubicin and Vincristine in Small Cell Lung Cancer: a Randomised Study

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From September 1986 until December 1991, 139 patients with histologically-proven small cell lung cancer, age < 75 years, performance status > 40, absence of brain metastases and no previous treatment, were randomised to receive either CEV cyclophosphamide 1000 mg/m² intravenous (i.v.), epirubicin 70 mg/m² i.v., vincristine 1.2 mg/m² i.v., every 3 weeks or PE (cisplatin 20 mg/m² i.v. and etoposide 75 mg/m² i.v. for 5 consecutive days, every 3 weeks) for six cycles. After three cycles, responding patients received radiotherapy to the chest (45 Gy/15 sessions) and to the brain (30 Gy/10 sessions—only in patients with limited disease achieving complete remission). 3 patients were ineligible. Patient characteristics included (CEV/PE) total number 66/70, median age 60/61 years, median performance status 80/80, extended disease 33/48 cases ($P = 0.04$). In evaluable patients, 42/62 (67.7%) responded to CEV while 42/58 (72.4%) responded to PE (P = non-significant); respective complete response rates were 16.1 and 29.3% (P = non-significant) and respective complete response rates in patients with extended disease were 9.4 and 28.9% ($P = 0.03$). Median survival was 10.5 months, without significant differences in the two treatment arms, even after adjustment for stage. PE was less well tolerated than CEV. Although PE is more active than CEV in certain subsets of patients, its apparent inability to improve survival in this and in other studies questions its routine use in small cell lung cancer.

Key words: small cell lung cancer, chemotherapy
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INTRODUCTION

CHEMOTHERAPY IS the mainstay of treatment of small cell lung carcinoma (SCLC), and response rates in the order of 60–90% with a 20–50% complete response rate are achieved by various chemotherapeutic regimens [1]. The combination of cyclophosphamide, doxorubicin and vincristine (CAV) was identified in the late 1970s as a relatively safe and effective treatment [1], and is also largely used because of its convenience and ease of administration. In more recent years, the combination of cisplatin and etoposide (PE) has been found to be active both as second-line [2, 3] and as induction treatment [4, 5]. In particular, a 5-day schedule of the PE combination yielded, in our hands [5], a 90% response rate (31% complete response rate) with a median survival of 15 months in limited disease (LD) and of 9.3 months in extended disease (ED). Particular interest was raised by the concept of alternating the two regimens which were supposed to be, at least partially, non cross-resistant. Alternating CAV and PE have been compared in randomised studies to CAV, and an