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Adjuvant Cisplatin-based Chemotherapy for Stage I and II Ovarian Cancer: a 7-year Experience

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87 patients with high risk of recurrence FIGO stage I and II ovarian carcinoma were treated with adjuvant chemotherapy consisting of cisplatin 50 mg/m^2 plus cyclophosphamide 600 mg/m^2 on day 1 every 28 days for 6 courses. Toxicity and efficacy of the regimen was evaluated after a median follow-up of 45 months. Treatment-related toxicity was mild and reversible, consisting chiefly of acute WHO grade 2 myelosuppression (10% of patients) and controllable grade 3 emesis (55%). No late toxicity was observed. Actuarial 7-year survival and relapse-free survival (RFS) were 76% and 61%, respectively; a statistically significant difference in outcome was observed for undifferentiated grade tumour (G1 vs. G2 vs. G3: $P < 0.01$) but not for FIGO stage disease (stage I vs. stage II). In our opinion, short-term chemotherapy including the most active single agent, i.e. cisplatin, appears a tolerable and effective treatment which deserves further evaluation in large randomised trials.
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INTRODUCTION

IN A REVIEW of literature from 1960 to 1975, the 5-year survival of FIGO stage I and II patients was only 70% and 32%, respectively, in spite of appropriate treatment for localised disease. The explanation of this failure was both related to the lack of accurate assessment of the extent of disease, and the poor understanding of the influence of prognostic factors on outcome of ovarian cancer. Results from staging studies indicated frequent understaging of early ovarian cancer with postsurgical residual disease in 33% and intraabdominal spread of disease in 75% of patients [1, 2]. Likewise, careful analyses about the prognostic importance of histological grade, positive peritoneal cytology and other factors demonstrated that conclusions of earlier clinical trials could be inaccurate because of maldistribution or poor definition of prognostic groups [3].

Thereafter, in the later 1970s it became apparent from natural history of "early" ovarian cancer that any form of adjuvant treatment must encompass the entire abdominal cavity. This finding accounted for the poor results achieved by surgery alone or postoperative pelvic irradiation [4].

Abdominopelvic radiotherapy, intraperitoneal chromic phosphate and alkyl-based chemotherapy have been employed to treat high-risk patients; results from these trials are conflicting [5, 6]. Cisplatin-based chemotherapy has proved to be the most effective treatment for advanced ovarian cancer, resulting in objective response rates up to 60–80% [7]. Therefore, chemotherapeutic regimens including the most active agent, i.e. cisplatin, are the best candidates to be tested in an adjuvant setting. Moreover, chemosensitivity of tumour cells correlates with growth fraction, which is particularly high in microscopic disease and is inversely proportional to tumour burden [8].

In a preliminary investigation we showed feasibility and efficacy of the cisplatin plus cyclophosphamide regimen in 41 patients with a median follow-up of 28 months [9]. In this paper we present the results of a larger series of patients enrolled and treated from 1982 to 1988 at the institutions collaborating with the Italian Oncologic Cooperative group GONO (the North-West Oncology Group).

PATIENTS AND METHODS

Eligibility criteria

Eligibility criteria for entering/treatment were: histologically confirmed epithelial ovarian carcinoma with high-risk prognostic factors (FIGO stage Ia G3, Ib G3, Ic, II); no macroscopic residual disease after first surgery; age 75 years or below; and ECOG performance status ≤ 2. Recent FIGO classification was adopted to define extent of disease [10]. Grade of tumour differentiation was established according to FIGO classification.

Surgical staging

For patients admitted to GONO institutions, surgery consisted of bilateral salpingo-oophorectomy, total abdominal hysterectomy, infracolic omentectomy, multiple random biopsies (diaphgramatic dome, bladder surface, vaginal cuff, anterior and posterior wall of the cul-de-sac, infracolic omental sites, mesentery and large and small bowel surfaces) and differential washings (suprahepatic spaces, lateral gutters and cul-de-sac). Pelvic and lomboaortic lymph-nodes were biopsied only if clinically suspicious.

Patients operated on prior to referral to GONO centres were submitted to chemotherapy and subsequently restaged with second-look surgery.

Chemotherapy

Within 1 month after surgery, patients received chemotherapy including cisplatin 50 mg/m^2 plus cyclophosphamide 600 mg/m^2 on day 1 every 28 days for 6 courses. Treatment was administered on an outpatient basis.

Patients were hydrated with 500 ml normal saline in 30 min, followed by cisplatin diluted in 1000 ml normal saline plus 2 g $MgSO_4$ in 60 min.

To reduce treatment-induced emesis, metoclopramide 1 mg/kg plus methylprednisolone 125 mg were administered prior to chemotherapy and repeated twice during the 24 h.

Second-look surgery

Operative re-exploration was not recommended as a routine procedure in those patients undergone careful initial surgical staging.

Second look included: peritoneal washings and random biopsies as described in primary laparotomy; removal of all internal genitalia and omentum in previously understaged patients; and removal of all resectable tumour deposits in case of relapse.

Investigations and follow-up

Full blood counts and complete biochemistry were performed before each therapy course. Global treatment toxicity was recorded every time. The required follow-up evaluations included physical examination, abdominopelvic sonography and serum CA-125 level every 3 months for the first 2 years, every 6 months up to 5 years and once a year thereafter.

Statistical methods

Survival and relapse-free survival (RFS) were calculated from the start of chemotherapy. All causes of death were included in survival curves; when RFS status was the endpoint, deaths other than those attributed to ovarian cancer or its treatment were censored if relapse had not occurred. The analysis of survival was conducted with the Kaplan–Meier method and the differences in such distributions were calculated by logrank test.

RESULTS

From January 1982 to December 1988, 87 patients entered the study. Their characteristics are listed in Table 1. Of the 87 patients, 52 (56.7%) were FIGO stage I and 37 (43.3%) stage II; noteworthy, the majority of patients had stage Ic disease (55.2%) and tumour of serous histology (43.7%).

All the patients were evaluable for survival, RFS and chemotherapy-related toxicity. 69 patients (79.4%) were staged through a correct surgical procedure as previously described while 15 (17.2%) were submitted to incomplete surgery. In 3 additional patients (young age, Ia stage) surgery was limited to monolateral oophorectomy to preserve fertility and staging procedures consisted of the forementioned methodical inspection of the entire abdomen plus biopsy of the remaining ovary.

83 of 87 patients included in the study completed treatment courses: 2 patients refused therapy; 2 patients discontinued

Table 1. Patients' characteristics

	No. of patients	%
Total	87	
Median age (range)	52 (25–74)	
Performance score (range)*	0 (0–1)	
FIGO stage		
Ia G3	3	3.5
Ib G3	1	1.1
Ic	48	55.2
IIa	7	8
IIb	11	12.6
IIc	17	19.6
Histology		
Serous	38	43.7
Mucinous	19	21.8
Endometrioid	15	17.2
Undifferentiated	5	5.7
Unclassified	2	2.3
Others	8	9.3
Grade		
G1	27	31.1
G2	32	36.8
G3	19	21.8
Unspecified	9	10.3
Surgery		
BSOH + omentum + random biopsies and washings	69	79.4
BSOH	15	17.3
Conservative	3	3.3

*ECOG performance status.
BSOH = bilateral salpingo-oophorectomy.

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Table 2. Toxicity

Toxicity	WHO grade 0	1	2	3
Nausea/vomiting	–	11	34	55
Mucositis	92	5	3	–
Leukopenia	84	7	10	–
Anaemia	93	5	1	–
Renal	100	–	–	–
Neurological	95	3	2	–
Alopecia	73	10	14	3

% of patients.

chemotherapy after four cycles, 1 patient because of cisplatin-related neurotoxicity (she regressed after chemotherapy discontinuation), and 1 patient because of cerebrovascular accident.

Treatment toxicity was acceptable. In fact, the major adverse events were emesis WHO grade 3 observed in 55% of patients, controllable with antiemetic treatment, and leukopenia WHO grade 2 in 10% of patients. In case of myelodepression (platelets $\leq$ 100 000, GB $\leq$ 2500) treatment course was delayed of 1 week or until recovery; in no case was drug reduction performed. No late toxicity was observed. All toxicities are detailed in Table 2.

After six courses of chemotherapy, 40 patients underwent second-look operation: selection of these patients was at the discretion of the responsible gynaecologist (30/69) or on the basis of previous incomplete surgical staging (10/15). Results of second-look surgery demonstrated positive findings in 7 patients (17.5%), all submitted to complete first surgery; persistence of microscopic disease in 5 stage Ic patients; and macroscopic nodular relapses in 2 cases. 10 patients out of the 33 with negative second-look relapsed after a median time of 15 months (range 2–49); only 3 of them had previously submitted to an incomplete staging procedure. None of the stage Ia or Ib patients had evidence of tumour at second-look.

After a median follow-up of 52 months (range 9–84), 16 patients died and 21 relapsed. 3/16 patients died without evidence of disease at 13, 15 and 20 months from the start of chemotherapy. In 1 case, a patient died following a reintervention because of acute bowel obstruction due to adhesive bands. The other 2 patients were 73 and 74 years old and died of cardiovascular accident. The 21 recurrences occurred after a median time of 20 months (range 5–77) from the start of chemotherapy. 1 case of stage Ia disease recurred after 44 months; the other relapses occurred in 8 patients with stage Ic (median DFS 20 months, range 6–77) and in 12 patients with stage II (median DFS 17 months, range 5–59).

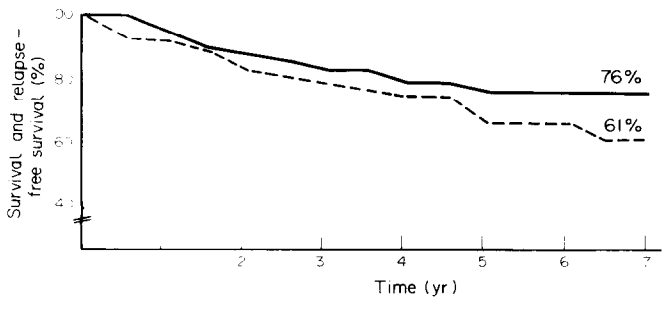

Fig. 1. 7-year survival (——) and relapse-free survival (-----) after treatment.

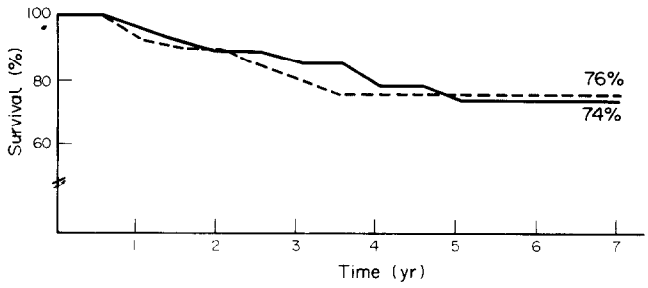

Fig. 2. Survival by stage: —— = stage I, ----- = stage II.

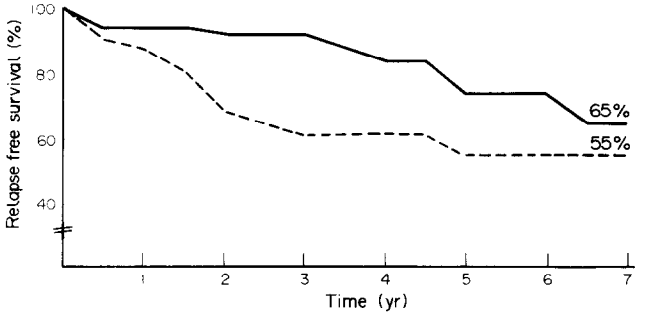

Fig. 3. RFS by stage: —— = stage I, ----- = stage II.

Actual 7-year survival and RFS were 76% and 61%, respectively (Fig. 1). When patients who underwent to incomplete surgical staging procedure were omitted from analysis, actuarial survival and RFS were 75% and 58%, respectively. The difference between this group and the entire patients population was not statistically evident (χ^2 = 0.95). No significant difference in survival and RFS was observed between stage I and II: survival = 74% and 76%, RFS = 65% and 55% for stage I and II, respectively (Figs 2, 3).

Probability of survival and RFS was analysed according to tumour differentiation: the curves demonstrated a statistically significant difference in survival ($P \leq 0.01$) with the worst prognosis for G3, compared to G1 and G2 (Figs 4, 5). No statistical difference in survival and RFS was evident when

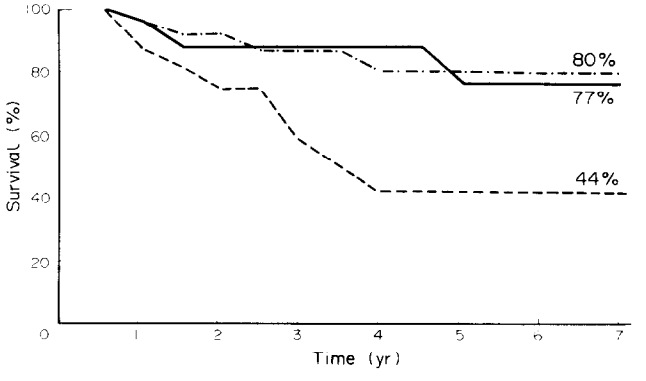

Fig. 4. Probability of survival by tumour differentiation: —— = G1, -·-·- = G2, ----- = G3.

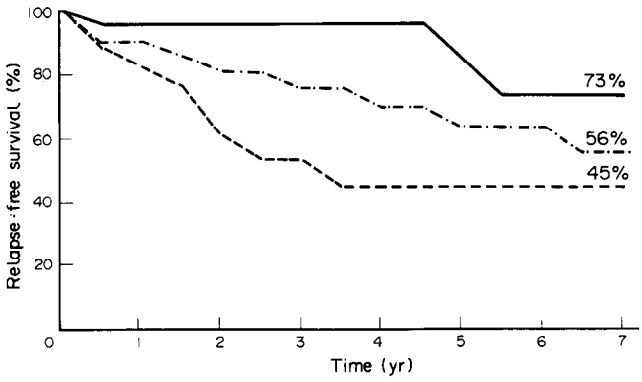

Fig. 5. Probability of RFS by tumour differentiation: —— = G1, -·-· = G2, ----- = G3.

patients were analysed according to age (over or under 50 years); actuarial 7-year survivals were 70% and 80%, respectively.

DISCUSSION

On the basis of the available information from studies on early ovarian cancer, the selection of therapy for stage I and II disease remains controversial. However general conclusions can be made.

Firstly, detailed staging has revealed that there is a group of patients for whom no treatment is indicated beyond total hysterectomy and bilateral salpingo-oophorectomy with no hystological evidence of cancer in the diaphragm, omentum, pelvic and paraaortic lymph-nodes and peritoneal cytology. The Ovarian Cancer Study Group and Gynecologic Oncology Group studies restricted this group to patients with stage IAi, IBi G1 or G2 ovarian carcinoma whose 5-year survival rate approximates 90% [1].

Secondly, the patterns of spread and sites of relapse of "early" ovarian carcinoma suggest that radiotherapy confined to pelvis alone is an inappropriate treatment modality [11].

The role of whole abdominal irradiation has yet to be clearly defined because of differences in treatment techniques, dose levels employed and selection criteria of patients. Moreover, the dose of radiation that can be given to the upper abdomen is considerably lower than those considered radical doses for solid tumours. Therefore, modest improvement in tumour control in the upper abdomen could be expected while curative effects would be seen in patients with microscopic disease confined to the pelvis. However, toxicity of abdominopelvic radiotherapy is relatively frequent and late bowel obstruction requiring surgical correction ranges from 1.4 to 14% [12]. While good results were obtained from Stanford University with the use of high-dose radiotherapy in stage II patients, Princess Margaret Hospital trials produced only 78% RFS in stage I [13].

Similarly, the lack of significant improvement in survival with the employment of intraperitoneal isotopes, the associated excessive toxicities and the difficulties of administration do not appear to make this treatment a good choice as adjuvant therapy [5].

Systemic chemotherapy alone or in combination with radiotherapy has been tested in the earlier studies but, since the introduction of cisplatin in medical practice, alkylating agents have proven to be no longer the optimal regimen for advanced epithelial ovarian cancer.

In 1982 we started a pilot study in patients with early ovarian cancer with a combination drug regimen including cisplatin and cyclophosphamide. The rationale was based on the superiority of combination chemotherapy including cisplatin over single agents and the potential usefulness of a short term, full-dose regimen in comparison with administration of a small dose of chemotherapy for a long period, with respect to efficacy and toxicity. In fact, evidence is now available that if neoplastic disease is not controlled in a limited number of cycles, it is unlikely that additional courses will produce cure; furthermore, that leukaemic potential of alkylating agents is correlated to total dose and duration of treatment.

Our results demonstrated a 7-year actuarial survival and RFS of 76% and 61%, respectively. Similar excellent results have been reported by Piver with the PAC regimen (cisplatin plus doxorubicin and cyclophosphamide) and by Bolis with cisplatin alone in stage I ovarian carcinoma [14, 15]. The lack of difference in survival and DFS between stage I and II in our study was probably due to the poor prognosis of stage Ic patients, who represented the majority of our patient population. Chemotherapy-related toxicity was mild and reversible. In our experience the six courses of chemotherapy were generally well tolerated and all patients were treated on an outpatient basis. No patient required dose reduction and acute myelosuppression was moderate, with prompt recovery within a week.

As confirmed by other studies, the role of second-look surgery in stage I and II ovarian carcinoma is questionable because 50% of relapses occurred in pathologically negative patients [16]. Therefore, routine second-look surgery can be spared in patients submitted to careful first staging procedures and appropriate adjuvant therapy.

Although firm conclusions could not be drawn from a non-randomised trial, the good results observed in 87 poor prognosis "early" ovarian cancer patients after a relatively long follow-up suggest that short-term chemotherapy with cisplatin and cyclophosphamide is a safe and effective treatment, which deserves further evaluation in large randomised trials.

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Long-term Effects in Skin and Thyroid after Radiotherapy for Skin Angiomas: a French Retrospective Cohort Study

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To evaluate the long-term effects of skin angioma irradiation, a recall programme was established which included the systematic recalculation of the radiation dose to the skin and the thyroid. 22% of the 6229 patients contacted had a dermatological examination which revealed cutaneous dystrophy in 81% of the 1137 exposed angiomas and in 39% of the 208 unexposed angiomas. The risk of dystrophy (telangiectasia, hypopigmentation, superficial and subcutaneous atrophy) was 12.1 higher ($P < 0.0001$) among patients who had received a surface skin dose above 30 Gy than among those who had received a dose of 10 Gy or less. The relative risk for each dystrophy component increased significantly ($P < 0.001$) with surface skin dose. Furthermore, 14 basal cell carcinomas (BCC) were observed in 12 patients from the exposed group for all quantities of radiation, with a mean latency period of 22 years. No BCC was observed for a surface skin dose below 10 Gy. Thyroid testing was done on a subgroup of 431 patients whose thyroid gland had been particularly exposed during angioma irradiation. After recalculation, the dose delivered to the gland was below 1 Gy in 98% of patients. Only 13 thyroid nodules were discovered (1 hot and 12 cold). 1 patient with a cold nodule had a malignant thyroid tumour 21 years after irradiation. He belonged to the group of 7 patients who had received a thyroid dose above 1 Gy. Although no morphological abnormality was found in 98% of the tested patients, most (92%) had a thyroid iodine content below 15 mg (the standard French value), while a raised serum thyroglobulin level (> 30 ng/ml) was observed in 17%. This might confer a higher risk of subsequently developing thyroid nodules.
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INTRODUCTION

THE STUDY of the late effects of radiotherapy is of major clinical interest, because radiation treatment may be responsible for various complications such as skin dystrophy, infertility, growth disorders and second primary malignant neoplasms [1]. However, such studies require large populations of exposed individuals adequately followed up over a long period of time, as well as accurate information on treatment administered sometimes several decades ago, in order to estimate doses delivered to the target organs. These two conditions are generally met in the evaluation of thyroid complications following ionising irradiation to the head and neck during childhood for an enlarged thymus gland, hypertrophic tonsils and sinusitis; a correlation has been found between the dose and the risk of thyroid tumour [2]. For other forms of radiotherapy such as the local application of radioactive plaques used to treat skin angiomas, it is more difficult to evaluate the dose received. Despite large cohort population studies, there has been no evaluation of possible dose response relationships for malignant tumours observed in different sites after irradiation of skin angiomas [3].

Ionising radiation was one of the treatments for haemangiomas until the 1960s when it was demonstrated that the majority resolve spontaneously in early childhood [4, 5]. Haemangiomas of infancy have been the subject of many studies at the Institut Gustave-Roussy (IGR) including a randomised therapeutic trial conducted between April 1961 and February 1963 to investigate