Pergamon

European Journal of Cancer, Vol. 33, Suppl. 1, pp. S31–S33, 1997

Printed in Great Britain
0959–8049/97 $17.00+0.00

PII: S0959-8049(96)00338-3

Gemcitabine in Ovarian Cancer: An Overview of Safety and Efficacy

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The outlook for patients with advanced ovarian cancer is still poor. Less than 30% survive for 5 years. The current standard chemotherapy is cisplatin-based combination treatment which gives response rates up to 70%. However, for patients who are resistant to cisplatin, new drugs are required. Response rates are generally low. Even with paclitaxel, remissions have been documented only in 16–30% of patients and with considerable toxicity. A number of studies using gemcitabine as a single agent in cisplatin-resistant patients have been completed or initiated and response rates of around 20% have been recorded. As gemcitabine is well tolerated, studies using gemcitabine combined with paclitaxel and cisplatin in ovarian cancer are ongoing or planned.

Key words: ovarian cancer, gemcitabine, efficacy, safety, review, clinical trials, chemotherapy
Eur J Cancer, Vol. 33, Suppl. 1, pp. S31–S33, 1997

INTRODUCTION

THE INCIDENCE of epithelial ovarian cancer is highest in the affluent countries of Western and Northern Europe and in North America where it is the fifth most common cause of death among women [1]. Epithelial ovarian cancer is difficult to treat and the 5-year survival rate for advanced disease is 30% or less. This is partly because early disease is often asymptomatic and, therefore, the disease is not diagnosed until it is in an advanced stage. Prognosis is influenced by both stage and by the postoperative residual tumour mass. Therefore, surgery is considered mandatory. Adjuvant systemic chemotherapy can improve outcome of ovarian cancer and is recommended in all stages except FIGO stage IA and IB of well-differentiated tumours. The most important predictive factors for response appear to be residual disease and tumour grade ($P < 0.001$), stage ($P = 0.002$), age ($P = 0.004$) and histological type ($P = 0.058$) [2].

Current chemotherapy of ovarian cancer

A number of drugs are active in ovarian cancer, including cisplatin, carboplatin, cyclophosphamide and doxorubicin. Cisplatin is generally regarded as the most active drug for the treatment of ovarian cancer and cisplatin-based chemotherapy is the current first-line of treatment with response rates up to 70% [3–5]. Treatment with either cyclophosphamide 750 mg/m^2 plus cisplatin 75 mg/m^2 every 3 weeks or cyclophosphamide 500 mg/m^2 plus doxorubicin 50 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks has been recommended as standard treatment. Carboplatin (which has fewer toxicity problems) may be used in place of cisplatin in patients with suboptimal stage III and stage IV ovarian cancer. However, in patients with good prognostic features, cisplatin-based treatment is still preferred. Treatment may be stopped in patients with a complete response (CR; including a normal CA-125) after six cycles and continued in patients with a partial response (PR). Second-line treatment may be necessary in patients whose disease stabilises or progresses. Patients who relapse after a treatment-free period may be retreated with a platinum-based regimen, but patients resistant to cisplatin will need alternative treatment with one of the new drugs.

New drugs

Although a number of dose-intensive regimens are being tested, the greatest hope for improving the survival of patients with ovarian cancer is the development of new drugs. Most interest has been focused on the taxanes (paclitaxel and docetaxel). These both have activity in ovarian cancer and paclitaxel is available as a second-line treatment if platinum-containing treatment fails. Objective response rates of up to 16–30% have been obtained in platinum-refractory patients [6, 7].

These studies evaluated a 3-h infusion. Myelotoxicity, predominantly neutropenia, is dose-limiting. Severe leucopenia, neutropenia or granulocytopenia occurs in around 18% of patients. When paclitaxel 110–200 mg/m^2 was administered over 24 h every 3–4 weeks, response rates increased to 20–48%. However, myelosuppression increased correspondingly, up to 100%. Hypersensitivity reactions to paclitaxel are common, although their occurrence may be reduced by pretreatment with a corticosteroid, an antihistamine and H_2-antagonists. Almost all patients suffer complete hair loss.

In a recently published study [8], a combination of paclitaxel with cisplatin seems to be superior to the standard cisplatin–cyclophosphamide regimen. This may become the standard treatment in the near future. In an ongoing German trial a

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Table 1. Characteristics of patients in the study conducted in the Netherlands and Denmark (E007)

	Number of patients (%)
Patients	50
Median age years (range)	58 (23–70)
Prior cisplatin treatment	48 (96)
Stage	
III	21 (42)
IV	29 (58)
Histological differentiation	
Well differentiated	3 (6)
Moderately differentiated	15 (30)
Poorly differentiated	20 (40)
Undifferentiated	2 (4)
Unknown	10 (20)
Tumour burden	
≤ 5 cm	15 (30)
> 5 cm	35 (70)
Treatment-free interval	
≤ 6 months	42 (84)
> 6 months	8 (16)
Performance status	
0	17 (34)
1	26 (52)
2	7 (14)

combination with paclitaxel and cisplatin is compared to paclitaxel and carboplatin.

Experience with gemcitabine

In preclinical studies, the novel nucleoside analogue, gemcitabine, has shown activity in a number of tumour models including ovarian cancer [9]. In an early phase II study, 2 of 7 eligible ovarian cancer patients responded to gemcitabine [10]. The activity of gemcitabine as a single agent is being evaluated in both previously treated and untreated patients with ovarian cancer.

Studies with gemcitabine as a single agent

The activity of gemcitabine as a single agent when given as second-line treatment is currently being evaluated in six phase II studies. In all studies gemcitabine is administered as a 30-min infusion once weekly for 3 weeks followed by a week of rest. Two of these studies have been completed.

Completed studies

14 patients were recruited to the first study (JHAJ, conducted in the U.S.). All patients had been heavily pretreated with regimens containing cisplatin or carboplatin. The starting dose of gemcitabine was 800 mg/m^2 and no responses were observed [11]. Patients in the second study (E007, conducted in the Netherlands and Denmark) had received one prior chemotherapy regimen or two regimens if one was used in an adjuvant setting [10]. Again, the starting dose was 800 mg/m^2. 50 patients were enrolled (Table 1). 8 patients were not evaluable for efficacy—4 patients refused treatment during or after the first course of gemcitabine and 4 patients were recorded as early deaths. Of 42 evaluable patients, 8 (19%, 95% CI 9–34%) achieved a PR with a median response duration of 8.1 months (4.4–12.5 months), with overall median survival of 6.2 months (0.2–26.0 months). It is important to note that most responders had poor prognostic factors (Table 2). 4 of these patients had not responded to prior platinum-based regimens. Gemcitabine was well tolerated: WHO grade 3 and 4 toxicity was 20.8% and 0% for leucocytes, and 10.4% and 2.1% for platelets. Non-haematological toxicity consisted mainly of mild transient rises in transaminases (WHO grade 1 and 2), mild flu-like symptoms (28% of patients) and peripheral oedema (22%).

Ongoing studies

There are four phase II studies of single-agent gemcitabine still in progress. The Netherlands/Denmark study has been extended to include stage III or IV patients with previously untreated ovarian cancer (study E007 extended, conducted in the UK and Denmark) [12]. A starting dose of 1250 mg/m^2 is being administered. This study is ongoing and, to date, 28 patients have been entered, of which 19 are currently evaluable for efficacy with four responses observed (Table 3).

Three other phase II studies with different inclusion criteria have started. Study 0027 is a Spanish/French/Australian study in previously treated patients. When entering the study, all patients must have progressive disease 1–24 months after one prior first-line platinum-based regimen. The starting dose of gemcitabine is 1200 mg/m^2. 37 patients have been enrolled with 4 PRs and 2 CRs in 32 evaluable patients (M. Friedlander, Prince of Wales Hospital, Sydney, Australia).

The second study is being conducted in Belgium, the Netherlands and Germany (study 0026). Patients have progres-

Table 2. Characteristics of responders (n = 8) in the study conducted in the Netherlands and Denmark (E007)

	Number of patients (%)
Stage IV	5 (63)
Poorly/undifferentiated tumours	6 (75)
Tumour burden > 5 cm	5 (63)
Treatment-free interval ≤ 6 months	8 (100)
Primary platinum resistance	7 (88)

Table 3. Characteristics of patients in the extended study conducted in the UK and Denmark (E007 extended)

	Number of patients (%)
Patients	28
Age range	42–77
Performance status	
0	5
1	16
2	7
Stage	
III	10
IV	16
Unspecified	2
Histological differentiation	
Poor	14
Moderate	8
Well differentiated	1
Unknown	5

sive, platinum-resistant disease with a relapse of 1–12 months after their last chemotherapy. They may have received two prior regimens postsurgery. The starting dose of gemcitabine is 1250 mg/m^2. Thus far, 41 patients have been enrolled, with 1 CR and 3 PRs in 14 evaluable patients [13].

The third study is recruiting patients who have received two prior regimens including platinum (first regimen) and paclitaxel (second regimen) (Italian/Australian study, JHBU). The starting dose is 1000 mg/m^2. Thus far, 25 patients have been enrolled with 2 PRs in 24 evaluable patients (M Mangoni, University of Parma, Italy). Activity has been seen in all these phase II studies.

Safety profile of single-agent gemcitabine

Data from completed studies using gemcitabine across a range of tumour types has been reviewed by Tonato and associates [14]. This analysis included 790 patients who received gemcitabine administered once a week for 3 weeks followed by a week of rest. Gemcitabine was remarkably well tolerated for such an active drug with few of the side-effects normally associated with cytotoxic agents. In particular, extensive myelosuppression is infrequent with modest WHO toxicity grades 3 and 4 for haemoglobin in 6.4% and 0.9% of patients, respectively, leucocytes in 8.1% and 0.5%, neutrophils in 18.7% and 5.7%, and platelets in 6.4% and 0.9%. Nausea and vomiting is mild and hair loss rare.

Studies with gemcitabine in combination with other drugs

Gemcitabine is a good candidate for use in combination with other drugs because of its activity, novel mechanism of action and good safety profile. Therefore, in addition to the single-agent studies, a phase I study of gemcitabine and paclitaxel in combination is underway in the U.K. and Sweden. Patients are allowed to have received up to one prior chemotherapy regimen. Thus far, 8 patients have been enrolled (age 40–75 years; all stage IIIc; Karnofsky scale 80–100, 7 pts, 60, 1 pt) (C. Poole, Queen Elizabeth Hospital, Birmingham, U.K.). The interval between last chemotherapy and starting treatment with gemcitabine varied between 1 and 10 months. Gemcitabine (1000 mg/m^2) was administered every week for 3 weeks on days 1, 8 and 15, followed by a week of rest. Paclitaxel (starting dose 135 mg/m^2) is given as a 3-h infusion on day 8 before gemcitabine. In the first cohort of 3 patients, 1 patient developed WHO grade 4 thrombocytopenia and another patient developed WHO grade 4 neutropenia in the absence of sepsis. Therefore, the dose was reduced to 100 mg/m^2 paclitaxel and 800 mg/m^2 gemcitabine. 5 patients have been treated at this dose level, which has been well tolerated. In Germany, a combination study of gemcitabine plus cisplatin as first-line treatment is soon to be started in women of 60 years and older.

DISCUSSION

It is difficult to evaluate new drugs for the treatment of ovarian cancer. From an ethical point of view, it is not acceptable to use new drugs as first-line treatments except in patients with the worst prognosis, i.e. those with bulky stage III or IV disease. Response to treatment must be assessed early enough to allow non-responding patients to be offered alternative treatment with a standard platinum-containing regimen. Therefore, new drugs are usually assessed in relapsed patients.

Gemcitabine is active in previously-treated platinum-resistant patients including those with the poorest prognosis. Activity has also been shown in previously untreated patients, and the response rate is comparable to those published for paclitaxel in similar patient populations. However, gemcitabine and paclitaxel have markedly different toxicity profiles and such indirect comparisons are difficult because the activity of these two drugs must be compared in a prospective randomised trial.

Gemcitabine has a novel mechanism of action and a mild side-effect profile and is, therefore, a good candidate for inclusion in combination chemotherapy regimens. Paclitaxel and platinum compounds are active in advanced ovarian cancer and combinations of these agents with gemcitabine would be of particular interest. Combinations of gemcitabine with cisplatin are effective in non-small cell lung cancer (Mosconi and associates, pages 54–173) and high efficacy of this combination in advanced ovarian cancer is expected.

1. Neijt JP, Allen DG, Colombo N. Carcioma of the ovary. In Peckham M, Pinedo HB, Veronesi U, eds. *Oxford Text Book of Oncology* 1995, 1293–1307.
2. Dembo AJ, Bush RS. Choice of post operative therapy based on prognostic factors. *Int J Radiat Oncol Biol Phys* 1982, **8**, 893–897.
3. International Federation of Gynaecology and Obstetrics, Annual report of the results of treatment in gynecological cancer. *Int J Gynaecol Obstet* 1989, **28**, 189–190.
4. NIH Consensus Conference. Ovarian cancer screening treatment and follow up. *J Am Med Assoc* 1995, **273**, 491–497.
5. Advanced epithelial ovarian cancer. 1993 consensus statements. *Ann Oncol* 1993, **4** (Suppl. 4), 83–88.
6. McGuire WP, Rowinsky EK, Rosenhein NB, *et al.* Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989, **111**, 273–279.
7. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy. *J Clin Oncol* 1994, **12**, 1748–1753.
8. McGuire WP, Hoskins WJ, Brady MF, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV in ovarian cancer. *N Engl J Med* 1996, **334**, 1–6.
9. Hertel LW, Boder GB, Kroin JS, *et al.* Evaluation of the anti tumor activity of gemcitabine (difluoro-2-deoxycytidine). *Cancer Res* 1990, **50**, 4417–4420.
10. Lund B, Hansen OP, Theilade K, Hansen M, Neijt JP. Phase II study of gemcitabine (2',2'-difluorodeoxycytidine) in previously treated ovarian cancer. *J Natl Cancer Inst* 1994, **86**, 1530–1533.
11. Morgan-Ihrig C, Lembersky B, Christopherson W, Tarassoff P. A phase II evaluation of difluorodeoxycytidine (dFdC) in advanced stage refractory ovarian cancer. *Proc Am Soc Clin Oncol* 1991, 10 (abstract No. 646).
12. Underhill C, Parnis FX, Highley M, *et al.* A phase II study of gemcitabine in previously untreated patients with advanced epithelial ovarian cancer (EOC). *Proc Am Soc Clin Oncol* 1996, **15**, 290 (abstract 795).
13. Kaufmann M, Bauknecht T, Jonat W, *et al.* Gemcitabine (GEM) in cisplatin-resistant ovarian cancer. *Proc Am Soc Clin Oncol* 1995, **14**, 272 (abstract No. 758).
14. Tonato M, Mosconi AM, Martin C. Safety profile of gemcitabine. *Anticancer Drugs* 1995, **6** (Suppl. 6), 27–32.

Acknowledgement—Studies were supported by research grants from Eli Lilly and Company.