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Phase II trial of tamoxifen and goserelin in recurrent epithelial ovarian cancer

J Hasan*, 1, N Ton1, S Mullamitha1, A Clamp1, A McNeilly2, E Marshall3 and GC Jayson1

1Cancer Research UK, Department Medical Oncology, Christie Hospital, Wilmslow Road, Withington, Manchester M20 4BX, UK; 2MRC Human Reproductive Sciences Unit, University of Edinburgh, Chancellor’s Building, Little France Crescent, Edinburgh EH16 4SB, UK; 3Department Medical Oncology, Clatterbridge Cancer Centre, Liverpool, UK

Endocrine therapy is a recognised option in the treatment of chemo-resistant ovarian cancer. We conducted a nonrandomised phase II evaluation of combination endocrine therapy with tamoxifen and goserelin in patients with advanced ovarian cancer that had recurred following chemotherapy. In total, 26 patients entered the study, of which 17 had platinum-resistant disease. The median age was 63 years and enrolled patients had received a median of three chemotherapy regimens prior to trial entry. Patients were given oral tamoxifen 20 mg twice daily on a continuous basis and subcutaneous goserelin 3.6 mg once a month until disease progression. Using the definition of endocrine response that included patients with stable disease (SD) of 6 months or greater, the overall response rate (clinical benefit rate) was 50%. This included one complete response (CR) (3.8%), two partial responses (PR) (7.7%) and 10 patients with SD (38.5%). The median progression-free interval (PFI) was 4 months (95% CI 2.4–9.6) while the median overall survival (OS) was 13.6 months (95% CI 5.5–30.6). Four patients received treatment for more than 2 years (range 1–31) and one of them is still on treatment. In none of the four patients was there any evidence of recurrent or cumulative treatment related toxicity. Treatment-limiting toxicity was not seen in any of the study population. Endocrine data demonstrated a marked suppression of luteinising hormone (LH) and follicle-stimulating hormone (FSH) to less than 4% of baseline values. No consistent correlation could be established between LH/FSH suppression and tumour response. Likewise no relationship was observed between Inhibin A/B and pro-alpha C levels and tumour response. Inhibin is unlikely to be a useful surrogate marker for response in locally advanced or metastatic ovarian cancer. Combination endocrine therapy with tamoxifen and goserelin is an active regimen in platinum-resistant ovarian cancer patients. Hormonal therapy is advantageous in its relative lack of toxicity, ease of administration and tolerability, thus making it suitable for patients with heavily pretreated disease, compromised bone marrow function and other comorbid conditions that contraindicate cytotoxic therapy as well as in patients with indolent disease.

Keywords: ovarian neoplasms; tamoxifen; goserelin

Ovarian cancer is the leading cause of mortality from gynaecological malignancies in the western world (Greenlee et al, 2001). Every year 5000 women die from this disease in the UK and 25 000 in the United States. Through the administration of platinum-paclitaxel chemotherapy after expert gynaecological surgery, recent trials have demonstrated a median survival of 3 years in women with advanced ovarian cancer (McGuire et al, 1996; Piccart et al, 2000). Over 70–80% of patients present with advanced disease (stage III/IV). The majority of these patients will develop recurrent disease from which they will die and new treatment strategies are needed. In particular, the management of platinum-resistant disease poses a major problem given the limited effectiveness of nonplatinum compounds in this setting. Patients have depleted bone marrow reserves in the presence of heavily pretreated disease and poor performance status that compound the complexity of the problem.

Clinical studies of endocrine therapy in ovarian cancer have evaluated a number of agents including antioestrogens, oestrogens, progestogens, aromatase inhibitors and GnRH agonists. Tamoxifen is one of the most extensively studied compounds among these. The mechanism by which tamoxifen works in ovarian cancer is not known; however, some data suggest that the antioestrogen effect is important as other antioestrogens inhibit ER+ ovarian cancer cells in vitro (Langdon et al, 1994). Several studies have shown a response rate of 10–20% with oral tamoxifen in patients with platinum-resistant ovarian cancer (Slotman and Rao, 1988; Hatch et al, 1991; Ahlgren et al, 1993). Two systematic reviews have reported response rates of 13 and 9.6% respectively (Williams, 2001; Perez-Garcia and Carrasco, 2002).

Owing to the close temporal relationship between the increase in incidence of ovarian malignancies and the rise in serum gonadotropin concentrations, it has been suggested that gonadotropins are also involved in the development of ovarian tumours (Emons and Schally, 1994; Imai et al, 1994). However, continuous stimulation of the pituitary by chronic administration of gonadotropin-releasing hormone (GnRH) agonists like gosere
inhibits the hypothalamic–pituitary–gonadal axis by downregula-
tion of the pituitary LH-RH receptors leading to suppression of
LH and gonadal steroid production. Furthermore, treatment of
patients with LH-RH, resulting in reduced gonadotropin concen-
trations has been associated with a 17% response rate in patients
with advanced disease (Kavanagh et al, 1989).

Trials of LH-RH agonists in ovarian cancer have shown
objective response rates ranging from 6.6 to 17.4% in various
studies with response durations of the order of a few months (Lind
et al, 1992; Sevelda et al, 1992; Paskevicute et al, 2002). Response
goserelin was not correlated to histological grading or other
tumor parameters. No significant treatment-related toxicities were
seen in any of the above studies.

We were interested in the apparent paradox that tamoxifen has
some antitumour activity in ovarian cancer whereas hormone
replacement therapy (HRT) is deemed safe in women who have
ovarian cancer (Eeles et al, 1991). One hypothesis to explain this is
that HRT decreases the release of LH, a known mitogen for ovarian
cancer; thus, the potential growth promoting effect of HRT is offset
by the reduction in LH, which is usually high in postmenopausal
women or in women who have undergone bilateral oophorectomy.
If this is correct then the addition of goserelin to tamoxifen should
be associated with greater anticancer activity. In keeping with
these preclinical studies, an antiproliferative activity of tamoxifen
was demonstrated in ovarian cancer cell lines. GnRH analogues
have direct inhibitory effects on ovarian tumour growth that are
distinct from the indirect steroid hormone-mediated effects (Emons
et al, 1989; Connor et al, 1994; Imai et al, 1994; Grundker
et al, 2000). These data suggest that the treatment of patients with
a combined antioestrogen (tamoxifen) and an LH suppressant
(goserelin) might improve the efficacy of endocrine therapy in
ovarian cancer. This study was therefore set up as a phase II
evaluation of combination endocrine therapy with tamoxifen and
goserelin in patients with advanced ovarian cancer.

Study design

This was an open label, nonrandomised phase II study designed
to determine the response rate (CR or PR or SD of greater than 6
months duration) and progression-free interval in patients with
advanced ovarian cancer treated with tamoxifen and goserelin. In
breast cancer the survival of patients treated with tamoxifen who
had stable disease (SD) for 6 months is the same as those who
attain a partial response (Howell et al, 1988). We therefore decided
to include patients who had SD of at least 6 months in our
definition of clinical response (clinical benefit rate). The study
protocol was approved by the local research ethics committee.
Both tamoxifen (Nolvadex®) and goserelin (Zoladex®) were
supplied by Astra-Zeneca. All patients gave informed consent
prior to trial entry.

Inclusion criteria

Patients were eligible if they had histologically proven epithelial
ovarian cancer that had progressed during or after completion of
at least one platinum containing chemotherapy regimen,
which usually included a taxane. Patients were also required to
have adequate haematological reserves (Hb ≥10 g dl−1, WBC ≥3 ×
10^3 l−1, Platelets ≥100 × 10^3 l−1), renal function (serum creatinine
<120 μmol) and liver function (serum bilirubin <30 μmol, AST/ALT
<2.5 × ULN in the absence of demonstrable liver metastases or
<5 × ULN in the presence of liver metastases). Patients must have
had a WHO performance status of 0–2 and bidimensionally
measurable disease on X-ray, ultrasound, CT or MRI that was
equal to or greater than 2 cm. Measurements must have been
made within 4 weeks of trial entry. Those who had prior endocrine
therapy for ovarian cancer were excluded, as were patients with

significant comorbidity and/or active brain metastases. Patients
were also required to stop HRT, immunotherapy or chemotherapy
4 weeks prior to trial entry.

Patient evaluation and treatment

Pretreatment evaluation consisted of a physical examination,
laboratory investigations as described above while additional
samples were taken for CA125 and hormonal analysis (LH, FSH,
inhibin A, inhibin B and pro-alpha C subunit of inhibin A).
A pretreatment staging CT scan was performed on all patients
at trial entry. Patients were reviewed at four weekly intervals for
laboratory investigations and clinical, toxicity and laboratory
assessment. Radiological evaluation was carried out every
3 months.

Patients were given oral tamoxifen 20 mg bd on a continuous
basis and subcutaneous goserelin 3.6 mg, once a month for 6
months. Treatment was continued beyond 6 months in patients
with stable or regressing disease until disease progression. No
patients were excluded from response analysis or toxicity
assessment. Response valuation was based on regression of
bidimensionally measurable disease on CT measurement of
tumours using WHO criteria.

Hormone assays

Plasma concentrations of LH and FSH were measured by radio
immunoassay previously described (Perheentupa et al, 2000),
with assay sensitivities of 0.8 and 0.9IU l−1, respectively,
and within-assay variabilities of 4.6 and 5.0%, respectively. Inhibin B
(Groome et al, 1996), inhibin A (Groome et al, 1994) and Pro-alpha
C (Groome et al, 1995) concentrations were measured using
two-site ELISA as described previously. The CV were <8% within
plate and <10% between plates for each of these assays with
sensitivities of 7.8 pg ml−1 for inhibin B, 2 pg ml−1 for inhibin A
and 5 pg ml−1 for Pro-alpha C.

Statistics

In total, 26 eligible patients were recruited to the study. The trial
was designed to be terminated if no responses were observed in the
first 14 patients. This scheme ensured that if the combination was
active in 20% or more patients, the chance of erroneously rejecting
the treatment after the first 14 patients was 0.044. Those who
showed evidence of clinical benefit were allowed to continue
treatment until disease progression, severe side effects or at
patient’s request to discontinue treatment.

Baseline characteristics

In total, 26 patients entered the study. The median age of patients
was 63 years (range 49–79). The median number of prior
treatment regimens was 3 (range 1–8). In total, 17 patients
had platinum-resistant disease, defined as disease progression
within 6 months of previous platinum therapy. Nine patients with
platinum-sensitive disease opted for the study in preference to
chemotherapy. Standard first-line therapy pre-1998 was carboplatin
and cyclophosphamide. Thereafter patients were treated with
carboplatin and paclitaxel unless taxanes were contraindicated
on medical grounds. Over 50% of the patients had poorly
differentiated tumours and multiple intra-abdominal disease sites
although only a third of patients had disease that exceeded 5 cm
diameter. Serous histology was the most common (50%). All
patients had evidence of progressive disease at trial entry. A
median of four cycles of treatment was administered per patient
(range 1–31).
DISCUSSION

In the only combination therapy study to date, Hofstra et al (1999) evaluated the efficacy of tamoxifen 20 mg a day and goserelin 3.6 mg each month in 25 patients with chemo-resistant disease. In this case the progression free interval was 5 months (2–96) and the median overall survival (OS) was 8 months (3–96). In our study, the combination of oral tamoxifen 20 mg bd and subcutaneous goserelin 3.6 mg once a month led to one CR (3.8%), two PRs (7.7%) and 10 patients with prolonged SD (38.5%). Interestingly, the patient with a CR had platinum-resistant disease at trial entry (treatment-free interval < 6 months) as did seven of 10 patients who had SD for 6 months. Data on the treatment–free interval for the two patients who experienced a partial response were unavailable. The median PFI was only 4 months, in keeping with the short response duration observed with other single-agent chemotherapy studies in this setting (Markman and Bookman, 2000). The median OS was 13.6 months with a substantial minority of patients surviving well beyond 2 years (Figure 1). Over a third of enrolled patients had SD for at least 6 months. The response rate and response duration observed in our study are significant given that the study group comprised of patients with adverse prognostic indicators and cannot be explained by selection bias or inclusion of patients with indolent disease. Indeed, the majority of patients recruited had biologically aggressive disease (>50% had platinum-resistant disease, significant tumour burden and poorly differentiated tumours. The former two being recognised adverse prognostic factors in advanced ovarian cancer). Three out of four patients who carried on with treatment for more than 2 or more years had platinum-resistant disease and multiple sites of disease. The majority of patients were heavily pretreated, having received a median of three previous chemotherapy regimens. All patients had radiological evidence of progression at trial entry.

As all patients had progressive disease at study entry, it is reasonable to conclude that combination endocrine therapy can control disease in a long-term fashion with minimal toxicity. Despite its modest efficacy, combination endocrine therapy offers an alternative option particularly in patients with heavily pretreated disease and limited bone marrow reserves and for patients with poor performance status who would not tolerate cytotoxic agents. The population recruited to this trial had received multiple courses of chemotherapy, and it would be interesting to evaluate the regimen in less chemo-resistant disease. Endocrine analysis as expected showed a significant suppression of LH and FSH levels. However, this did not correlate with clinical response to treatment. This is in keeping with findings from recent studies that indicate the classical LH-RH receptor signal transduction pathways known to operate in the pituitary are not involved in mediating the antiproliferative effects of LH-RH analogues. Instead, these agents exert their antimitogenic effect through interference with the signal transduction of growth-factor receptors and related oncogene products associated with tyrosine-kinase activity. The mechanism of action is probably an LH-RH-induced activation of a phosphotyrosine phosphatase, counteracting the effects of receptor associated tyrosine kinase (Emons et al, 1998). The antiproliferative effect of GnRH analogues is also dose-dependent. Higher tissue concentrations achieved by escalating dosing regimens or alternative routes of administration may yield better responses and requires further evaluation (Emons and Schulz, 2000).

The significance of secretion of functional inhibin by epithelial ovarian cancers is not clear. Elevated serum inhibin levels have been noted in postmenopausal women with ovarian tumours (Healy et al, 1993) and it has been suggested that inhibin may have a role as a tumour marker, particularly when used in combination with CA125 (Robertson et al, 1999). Elevated serum inhibin and pro-alpha C levels have been reported in patients with GCTs and mucinous tumours of the ovary (Healy et al, 1993; Jobling et al, 1994; Boggess et al, 1997). Serum inhibin has never been evaluated as a marker for response to treatment in epithelial ovarian cancer although a small series has evaluated it in monitoring response to...
GnRH analogues in GCT (Kauppila et al, 1992). Available data show that inhibit assays, which detect all inhibin forms, that is, assays that detect the alpha subunit both as the free form and as an alpha-beta subunit dimer, provide the highest sensitivity and specificity for diagnosing ovarian cancer (Robertson et al, 2002). We therefore prospectively evaluated serum inhibit (inhibit A (alpha-betaA), inhibit B (alpha-betaB)) and pro-alpha C as potential surrogate markers of response to endocrine therapy in patients with advanced epithelial ovarian cancer. In our study, no relationship was observed between serum inhibit A/B and pro-alpha C levels and clinical response. An initial suppression of pro-alpha C levels was noted in all patients on whom data were available. The clinical significance of this remains unclear. It has been suggested that elevated serum inhibit levels in epithelial ovarian cancers are a consequence of production and secretion by the stroma rather than epithelial tumour cells (Zheng et al, 2000). Serum inhibit levels correlate with the extent of stroma, with stroma in mucinous tumours and sex cord tumours being more extensive than in other histological subtypes. Thus, while serum inhibit may be a useful marker for epithelial ovarian tumours confined to the ovary, it may not be appropriate in monitoring disease or response to treatment when the tumour has metastasised to other tissues.

CONCLUSION

Combination endocrine therapy with tamoxifen and goserelin is an active regimen in platinum-resistant ovarian cancer patients. Hormonal therapy is advantageous in its relative lack of toxicity, ease of administration and tolerability, thus making it suitable for patients with heavily pretreated disease, compromised bone marrow function and other comorbid conditions that contraindicate cytotoxic therapy as well as in patients with slowly progressive disease. Prolonged survival was noted in some patients and response rates were similar to those observed with other single-agent chemotherapy, although prospective randomised studies need to be performed to confirm the superiority of this regimen.

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