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ORIGINAL ARTICLE

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Tomudex (ZD1694, NSC 639186) in platinum-pretreated recurrent epithelial ovarian cancer: a phase II study by the Gynecologic Oncology Group

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Abstract *Purpose*: Tomudex is a second-generation folate analogue that when polyglutamated is a potent inhibitor of thymidylate synthase (TS). *Methods*: Based on indications of antitumor activity in phase I trials, the Gynecologic Oncology Group initiated a phase II study of Tomudex 3 mg/m^2 intravenously every 3 weeks in patients with epithelial ovarian cancer, who had been pretreated with platinum drugs, and had subsequently recurred more than 6 months following such treatment. *Results*: Of 30 patients entered into the trial, 2 were pathologically ineligible, leaving 28 fully evaluable. In this patient population, Tomudex was generally well tolerated, but only three objective (partial) responses were documented. *Conclusions*: With the level of activity seen, the drug was not considered for further clinical development in ovarian cancer by the Gynecologic Oncology Group. However, it may be worthwhile to explore whether quantitation of TS could lead to selection of patients more likely to respond to this TS inhibitor.

Key words Thymidylate synthase · Antifolates · MOv18 antibody · Cisplatin-sensitive ovarian cancer

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Introduction

Following development and initial clinical study of CB3717, a quinazoline inhibitor of thymidylate synthase (TS), interest was generated in synthesizing a derivative retaining the activity against adenocarcinomas but avoiding unpredictable hepatic and renal toxicities presumably related to insolubility [2, 7, 9]. Tomudex (ICI D1694, ZD1694, NSC 639186) is such a second-generation folate analogue that was selected for clinical study as a selective inhibitor of TS, a key enzyme in the DNA synthetic pathway [5, 8–10]. This inhibition takes place via Tomudex polyglutamates that are formed by the action of folypolyglutamate synthetase (FPGS) [5]. Moreover, these polyglutamates have prolonged intracellular retention leading to potency, and probably account for selectivity against certain cancers. In preclinical studies, Tomudex has been shown to be cytotoxic in a number of tumor cell lines, and to show superior activity against human tumor xenografts compared with 5-fluorouracil (5FU) and methotrexate [17]. In the initial clinical studies, activity against colorectal cancer was noted, and this led to phase III studies comparing Tomudex with 5FU and leucovorin [15]. Some activity has been noted against a number of other tumor types, including ovarian cancer [6, 15]. This stimulated the Gynecologic Oncology Group (GOG) to

perform a phase II study in patients with relapsed ovarian cancer.

Materials and methods

A cohort of patients who were still potentially sensitive to platinum compounds (i.e. they relapsed 6 months or longer after their initial induction platinum-based treatment) were selected for entry into GOG protocol #146-B. Treatment with paclitaxel in a separate regimen, if not given earlier, was also allowed prior to entry. At least 3 weeks had to elapse from cessation of other treatment to study entry. A GOG performance status of 3 or better was required. All patients were to have normal bone marrow function (white blood cell count $>3000/\mu l$, platelets $>100\,000/\mu l$, granulocytes $>1500/\mu l$), renal function (creatinine <2.0 mg/dl) and hepatic function (bilirubin, AST, and alkaline phosphatase less than twice the institutional normal). Following reports of adverse drug events associated with renal dysfunction in other trials of Tomudex, a normal serum creatinine at entry and at redosing was required thereafter. Patients were specifically warned not to ingest any folate-containing vitamin supplements during the period of study. Written signed informed consent approved by the Institutional Review Boards was required prior to registration.

Patients were treated with Tomudex at an initial dose of 3 mg/m^2 to be repeated every 3 weeks in the absence of clinical progression. The drug was administered as a 15-min infusion at a various concentration in the range 0.002 to 0.2 mg/ml. Prior to every course, patients underwent a pelvic examination. Radiologic scans of the abdomen and pelvis were required every 8 weeks if disease was only measurable by such means. All patients had measurable disease. Standard GOG response criteria were used [1]. Patients showing responses or stable disease could be continued indefinitely at the investigator's discretion as long as no severe side effects were apparent. Hematologic parameters were followed weekly, serum chemistries every 3 weeks, and objective disease assessments including CA-125 every 6 weeks. Dose modifications for hematologic and/or gastrointestinal toxicities were prescribed as shown in Table 1. Dose delays were also prescribed if these or other toxicities had not resolved by day 21 of the cycle. Liver enzymes were not required to return to normal, but if they were twice normal, they had to show improvement by the following week prior to redosing.

Results

The study began in April 1994 and was closed to patient accrual in May 1995 after 30 eligible patients had been entered. Two patients were pathologically ineligible; one did not have an ovarian primary and one had insufficient pathologic documentation; 28 patients were therefore fully evaluable and received 122 cycles. The median number of cycles given was 3.5 (range 1–23). Patient characteristics are displayed in Table 2. Three patients (10.7%, 95% confidence interval 2.3–28.2) achieved partial responses (PR) that lasted 5.8, 8.1 and 27.0+ months. At the time of first assessment, 14 patients had stable disease, whereas 11 had increasing disease. Of the 14 patients with stable disease and 2 with PR, 5 remained on study for the longest periods having received from 6 to 23 cycles of Tomudex. The median survival for all patients was 20.1+ (4.5–29.2) months.

Severe toxicities, as expected, were primarily hematologic with three grade 4 and two grade 3 neutropenia; two patients also manifested grade 3 thrombocytopenia. These led to dose modifications; hematopoietic growth factors were not used. One patient each experienced grade 3 and 4 nausea and vomiting. Gastrointestinal toxicity was otherwise rare with grade 2 and 1 diarrhea being recorded. No stomatitis was noted. Other grade 3 toxicities included fatigue in three patients; anemia, skin rash, and AST (SGOT) elevation in one each. Two patients experienced fever, two additional patients had skin rashes and minor degrees of anemia or transaminase elevations were seen in six and five, respectively. One patient declined to receive the drug after her initial dose because of skin rash and weakness. Four patients had dose delays as a result of toxicity, and three patients required dose modifications. At the other extreme, another patient received 23 cycles with excellent tolerance.

Table 1 Dose modifications for gastrointestinal and/or hematologic toxicity (– no further treatment)

Hematologic toxicity (grade)	Dose				
	Gastrointestinal toxicity (grade)				
	0	1	2	3	4
0	100%	100%	75%	50%	–
1	100%	100%	75%	50%	–
2	100%	75%	50%	–	–
3	75%	50%	50%	–	–
4	50%	50%	0%	–	–

Table 2 Patient characteristics

Characteristic	No. of cases
Age (years)	
Median	60.5
Range	44–79
GOG performance status	
0	16
1	7
2	5
Tumor grade	
1	1
2	10
3	17
Site of disease	
Pelvic	13
Extrapelvic	15
Prior radiotherapy	2
Prior chemotherapy	
One regimen	2
Two regimens	26[a]

[a] 24 patients received previous paclitaxel

Discussion

The response rates noted in this trial and in another trial in a similar group of patients with ovarian cancer have indicated only modest activity of Tomudex in this disease [4, 6]. This degree of activity is comparable to that

of 5FU and leucovorin in a similar population of pretreated patients [12–14]. Although disappointing, the antitumor effects observed do support efforts at identifying retrospectively some pharmacodynamic correlates of response to justify future trials or drug development of similar compounds against this cancer.

Interest in Tomudex and related compounds continues because of the possibility that one may identify patients likely to benefit by studying TS expression in ovarian tumors. In a number of studies, a low level of TS has predicted responsiveness to 5FU and to other TS inhibitors [11]. In addition, as a folate antimetabolite, the possibility of enhancing its effects through selective modulation may be raised. Tumors that have high levels of FPGS and are able to retain the Tomudex polyglutamates may be more susceptible to inhibition of nucleoside uptake. Presumably, in such tumors the only way for cells to survive the TS inhibition is through thymidine uptake. Yet another feature that may impart some selectivity for antifolates in some ovarian cancers is the presence of the folate-binding protein identified by MOv18 and MOv19 monoclonal antibody reactivity at the cell surface [3]. Whether MOv18 immunostaining might predict for enhanced uptake of Tomudex and related antimetabolites, leading to greater cytotoxicity against tumors expressing this folate-binding protein, is currently unclear [16]. It is hoped that a study will be done of patients' tumors for their expression of TS and MOv18, with the aim of casting further light onto some of these issues.

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