Phase I Trial of ZD9331, a Nonpolyglutamatable Thymidylate Synthase Inhibitor, Given as a 5-Day Continuous Infusion to Patients with Refractory Solid Malignancies

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ABSTRACT

Purpose: This dose-escalating study investigated the toxicity, pharmacokinetics, and efficacy of the novel direct-acting antifolate ZD9331, given as a 5-day i.v. infusion every 3 weeks.

Experimental Design: Forty-five patients with refractory solid malignancies received ZD9331, which was escalated from 0.125 mg/m²/day.

Results: Dose-limiting grade 4 thrombocytopenia occurred in 3 of 6 patients treated at 8 mg/m²/day; other drug-related toxicities, across dose levels, included skin and gastrointestinal toxicity, lethargy, and asymptomatic, reversible, elevated transaminases. The maximum plasma concentration and area under the curve increased with dose. Clearance was dose-dependent and predominantly renal. At doses ≥2.4 mg/m²/day, plasma 2'-deoxyuridine levels were elevated consistently indicating inhibition of thymidylate synthase. Two patients had a partial response (breast, 1 patient; ovarian, 1 patient), and 10 patients had stable disease.

Conclusion: The maximum tolerated dose was defined as 6 mg/m²/day, and the toxicity profile for this regimen was considered acceptable and manageable. Administration of ZD9331 lead to elevation of 2'-deoxyuridine levels, signifying thymidylate synthase inhibition, and evidence of antitumor activity was observed.

INTRODUCTION

ZD9331 is a novel, direct-acting antifolate and a product of rational structural design. It is a specific TS inhibitor and was developed for the treatment of solid malignancies (Fig. 1; Ref. 1). TS is an essential enzyme for DNA synthesis and, hence, a valid target for the development of new anticancer drugs (2, 3). 5-Fluorouracil is an example of a nonspecific inhibitor of TS; folate-based, specific TS inhibitors have been developed, such as raltitrexed (“Tomudex”), which has been approved as first-line treatment for advanced colorectal cancer in the United Kingdom (4, 5).

Some antifolate TS inhibitors are metabolized to more potent polyglutamate forms by FPGS (6). Therefore, tumors with low FPGS levels or high folylpolyglutamyl hydrolase activity may be resistant to those TS inhibitors requiring polyglutamation (7). Preclinical in vitro studies have demonstrated that ZD9331 is not a substrate for FPGS (8), because of substitution of the γ carboxyl group on glutamic acid by a tetrazole group, as shown in Fig. 1. These studies have also shown that this compound has a broad spectrum of activity (8). In dogs, the dose-limiting toxicities of ZD9331 were hematological and gastrointestinal (1).

Because of the pharmacokinetic profile of ZD9331 in both rodents and in dogs as well as the lack of polyglutamation, it was expected that prolonged exposure would be required for optimal antitumor activity. This study investigated a 5-day continuous i.v. infusion schedule, whereas an alternative regimen, a 30-min i.v. infusion daily for 5 days, was also studied (9).

The primary objective of this study was to determine the dose-limiting toxicities of ZD9331 in humans, when given as a 5-day continuous i.v. infusion every 3 weeks, and to define the MTD. The secondary objectives were to determine the pharmacokinetics, toxicity profile, and antitumor activity of ZD9331 when administered in this schedule.

PATIENTS AND METHODS

Patients

All of the enrolled patients met the following inclusion criteria: age ≥18 years, histological/cytological confirmation of a solid malignant tumor, incurable disease refractory to standard therapies, WHO performance status ≤2, and life expectancy >12 weeks.

Patients were excluded from the study if they had a WBC count <3.5 × 10⁹/liter, absolute neutrophil count <2.0 × 10⁹/liter, platelets <100 × 10⁹/liter, bilirubin >1.25 × ULN, AST/ALT >2.5 × ULN (>5 × ULN in patients with liver metastases), or creatinine >1.25 × ULN. Additional exclusion criteria: age ≥70 years, active hepatic or brain metastases, prior malignancy, COPD, active peptic ulcer disease, diabetes, uncontrolled hypertension, autoimmune disease, or prior treatment with TS inhibitors.

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Note: The abbreviations used are: TS, thymidylate synthase; FPGS, folylpolyglutamate synthase; DLT, dose-limiting toxicity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC₀−₅, area under the plasma concentration-time curve; Cₘₚ, maximum plasma concentration; t₁/₂, terminal elimination half-life; Vₘ, volume of distribution at steady-state; CL, plasma clearance; CL₆₃, renal clearance; dUrd, 2'-deoxyuridine.

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criteria were: severe systemic disease, systemic anticancer therapy within the previous 4 weeks (6 weeks for nitrosoureas and mitomycin C), concomitant folic acid, extensive radiotherapy in the preceding 6 weeks, incomplete recovery from surgery, active brain metastasis, and pregnancy or breast feeding.

Recruitment for this study, which was undertaken at the Royal Marsden Hospital, commenced in May 1996. The study was conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice. The protocol was approved by the Research Ethics Committee of the Royal Marsden Hospital. Informed written consent was obtained from all of the patients before treatment began.

**Trial Design and Treatment Regimen**

This was an open, noncomparative, two-stage dose-escalation trial of a 5-day continuous i.v. infusion of ZD9331. ZD9331 was administered in 5% dextrose, via a peripheral or central vein, at a starting dose of 0.125 mg/m²/day. In the first stage, the dose was doubled until any drug-related toxicity (except nausea, vomiting, or alopecia) was seen in any patient at a given dose level. When this was observed, the second-stage dose-escalation scheme began, with a minimum of 3 patients treated at each dose level. Escalation then followed a modified Fibonacci scheme until the dose at which 3 patients (with ≥6 treated at that level) had any of the following: grade 4 neutropenia with fever or grade 4 neutropenia without fever for ≥7 days; grade 4 thrombocytopenia or grade 3/4 nonhematological toxicity (other than transient, reversible elevations of liver transaminases) that was not ameliorated by symptomatic measures. This was then defined as the dose at which DLT occurred. The MTD was defined as a dose below that which resulted in DLT that caused acceptable, manageable, and reversible toxicity, and could be recommended for Phase II evaluation.

Patients received two cycles of treatment unless there was clear evidence of disease progression or clinical deterioration. Patients with an objective response to treatment were allowed to continue until a withdrawal criterion was met or they chose to discontinue.

Hematological and biochemical parameters were reassessed before each planned treatment cycle and, if necessary, additional treatment could be delayed for ≤21 days. Treatment was halted if grade 2–4 drug-related hematological toxicity (neutropenia or thrombocytopenia) or nonhematological toxicity (except nausea, vomiting, alopecia, moderate lethargy, or transient, reversible elevations of ALT or AST) was noted during the infusion. Dose reduction was permitted if there was evidence of clinical benefit with significant toxicity. At the discretion of the physician, intrapatient dose escalation was permitted.

The prophylactic use of antiemetics was not permitted before the time of the first dose of ZD9331 until grade 2–4 nausea or vomiting was observed in ≥3 patients during the first treatment cycle. Prophylactic antiemetics could then be given during the first treatment cycle at higher doses and were allowed (but not recommended) after cycle 1 at all of the dose levels.

**Assessment Methods**

**Tolerability.** Patients were assessed for toxicity on a weekly basis throughout each cycle of treatment. Toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria version 1.0.

**ZD9331 Pharmacokinetics.** Blood samples for pharmacokinetic analysis were taken from all of the patients in cycle 1 and in 1 patient per dose level at doses ≤1.6 mg/m²/day during cycle 2. Samples were collected preinfusion: 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h after commencement of infusion; and 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 h, and 9 and 16 days (±2 days) after cessation of the infusion. In addition, 24-h urine samples were collected on days 1 and 5 of cycle 1.

Plasma and urine concentrations of ZD9331 were measured by high-performance liquid chromatography with tandem mass spectrometry and were used to derive the following pharmacokinetic parameters: AUCₜ₀₋ₚ₀, Cₘₐₓ, t₁/₂, Vₘ, CL, and CLₚ.

**dUrd Analysis.** Blood samples (5 ml) were collected on days 1, 2, 4, 6, 8, and 15 during the first cycle of treatment, for analysis of plasma dUrd, which was measured using high-performance liquid chromatography (10).
Tumor Assessment. Tumor assessments were performed within 4 weeks before entry, after cycle 2, every second cycle thereafter, and at withdrawal. Lesions were identified as measurable, evaluable but not measurable, or neither measurable nor evaluable, according to Union Internationale Contre le Cancer/WHO criteria. A complete response was defined as no clinical, radiological or biochemical evidence of residual lesions maintained for 4 weeks. A partial response was defined as no evidence of disease progression (with a decrease of ≥50% in the sum of the products of the two largest perpendicular diameters of all of the measurable marker lesions) or improvement in the evaluable lesions (based on radiological or photographic evidence maintained for 4 weeks). Disease progression was confirmed by the presence of new lesions or an increase of >25% in an existing lesion. Stable disease was defined as no objective disease progression or response amounting to a partial response.

Blood samples were taken for tumor markers (carcinoembryonic antigen or CA125) at baseline, following cycle 2, and every second cycle thereafter, in patients with suitable tumors; a decrease of >50% was considered indicative of antitumor activity.

RESULTS

Patients. Forty-five patients with solid tumors were recruited between May 1996 and March 1999 (Table 1). The patients had a mean age of 53.3 years and mainly had WHO performance status 1 or 2 (93%). Thirty-one patients (69%) had previously received ≥2 different chemotherapy regimens. Eight patients (18%) had locally advanced disease alone, and 37 (82%) had metastatic disease.

Dose Levels. The patients were recruited to 13 dose levels (Table 2). A total of 116 cycles of chemotherapy were administered. Individual patients received one to six treatment cycles (median, two; Table 2). Six patients received the 6 mg/m²/day dose level because 1 of the first 3 patients had DLT (grade 4 thrombocytopenia and neutropenia) at this dose. Intrapatient dose escalation occurred in 1 patient with stable disease and no significant toxicity; the dose was escalated from 0.125 to 0.25 mg/m²/day in cycle 6. Treatment was delayed >7 days because of toxicity in 2 patients (receiving ZD9331 2.4 and 4 mg/m²/day, respectively); the second of these patients had undergone a dose reduction from 6 to 4 mg/m²/day in cycle 2 because of grade 4 thrombocytopenia and grade 3 neutropenia.

Tolerability. Hematological toxicity was minimal at doses ≤4 mg/m²/day (Table 3). DLT occurred at 8 mg/m²/day, with 3 patients at this dose level experiencing drug-related grade 4 thrombocytopenia (Table 3). Two patients had grade 4 thrombocytopenia and grade 3 neutropenia, one of whom also had grade 4 diarrhea, and the third patient had grade 4 neutropenia and thrombocytopenia. Five patients at 8 mg/m²/day had grade 2 anemia. Both thrombocytopenia and neutropenia were reversible and manageable.

Nonhematological toxicity was minimal for the first 11 dose levels (Table 3). Reversible asymptomatic elevation of transaminases was seen at all of the dose levels. One patient at 1 mg/m²/day had grade 4 elevated transaminases but progressive liver metastases were confirmed by computed tomography scan after cycle 1; transaminases returned to baseline (grade 2) on discontinuation of ZD9331, and the patient was withdrawn from the study. Grade 3 nausea occurred in 3 patients at dose levels 0.6 (1 patient), 4 (1 patient), and 8 mg/m²/day (1 patient). One patient at 8 mg/m²/day had grade 4 diarrhea combined with hematological DLT. Stomatitis became more frequent at higher dose levels (Table 3). A self-limiting erythematous, pruritic, macular rash occurred in 7 patients at dose levels 4–8 mg/m²/day, but only 1 patient had a grade 3 rash (Table 3). Grade 1 alopecia occurred sporadically, and some patients developed erythema at the cannulation site. Sixteen patients reported grade 1–2 lethargy.

Eight patients died during the study; the primary cause of death in 7 cases was disease progression, whereas in 1 patient death was primarily attributed to bronchopneumonia, but disease progression was recorded as a secondary cause. This death occurred at the end of the 28-day follow-up period. This patient...
had been identified to have progressive disease several weeks earlier. He had tolerated the infusional ZD9331 very well with no evidence of myelosuppression and generated a marked leucocytosis in response to this terminal illness. Thus, this was not considered to be a drug-related death.

Pharmacokinetics. At the initial dose levels, the plasma concentration of ZD9331 increased throughout the 120-h infusion period. Steady state was not achieved for the lower doses but was seen in 75% of patients treated at the two highest doses (6 and 8 mg/m²/day). After the end of the infusion, ZD9331 plasma levels declined biexponentially (Fig. 2). Low but detectable concentrations were still present on day 15 at all of the dose levels and on day 22 after doses ≥0.25 mg/m²/day. The mean terminal t 1/2 for all of the patients was 75.5 h (± SD 25 h). Exposure to ZD9331 increased with increasing dose; however, this was not dose-proportional; over the 64-fold increase in dose during the trial, there was an increase in mean AUC and C max of 22- and 28-fold, respectively (Table 4). The nonlinearity in exposure was a result of the increase in CL with increasing dose (Table 4); mean CL increased ~3-fold (from 3.46 to 10.11 ml/min) over the dose range investigated.

A comparison of the pharmacokinetic parameters of ZD9331 during cycles 1 and 2 is presented in Table 5. There was little intrapatient variability in CL, V ss , and t 1/2 between the two cycles. In addition, although measurable levels of ZD9331 were still detectable before cycle 2, there was no consistent increase in C max or AUC during cycle 2.

As a consequence of the slow CL of ZD9331, CL R was determined only on day 5. The calculation for CL R assumed that steady-state had been achieved; hence, values for the low doses are approximations, whereas at the higher doses (where steady-state was achieved in some patients) the values of CL R can be viewed with greater confidence. The relationship between AUC and dose (in cycle 1) is presented in Fig. 3.

Pharmacodynamics. The mean baseline deoxyuridine levels for patients treated at the 1.6–8 mg/m²/day dose levels

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**Table 3** Highest CTC grade of adverse events per dose level

<table>
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<th>Adverse event</th>
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a One patient had progressive liver metastases after cycle 1; liver transaminases returned to baseline (grade 2) on discontinuation of ZD9331.
b Thrombocytopenia (grade 4), neutropenia (grade 4), and diarrhea (grade 1).
c Thrombocytopenia (grade 4) and neutropenia (grade 4; 1 patient); thrombocytopenia (grade 4), neutropenia (grade 3), and diarrhea (grade 4; 1 patient) and thrombocytopenia (grade 4) and neutropenia (grade 3; 1 patient).
was 57.0 nM (±SD 28.19 nM). Mean percentage changes in dUrd over the course of cycle 1 were calculated for these patients. Plasma dUrd levels showed little change during treatment at 1.6 mg/m²/day. At higher doses of ZD9331, more constant elevations were seen. At doses of 6–8 mg/m²/day, plasma dUrd levels rose rapidly and remained elevated for up to 2 weeks (Fig. 4).

**Antitumor Activity.** Of the 37 evaluable patients, 25 had marker lesions and 12 had nonmarker lesions only. Two patients had a partial response (breast and ovarian cancer), the first occurred at 0.6 mg/m²/day and the second in the patient with ovarian cancer occurred at 6.0 mg/m²/day. An additional patient with ovarian cancer also achieved a 72% fall in CA125 from baseline after cycle 2, which was maintained after cycle 4 but had disease progression after cycle 6. Ten patients had stable disease, 4 of whom (breast, 2 patients; renal, 1 patient; and head and neck, 1 patient) had stable disease was 57.0 nM (±SD 28.19 nM). Mean percentage changes in dUrd over the course of cycle 1 were calculated for these patients. Plasma dUrd levels showed little change during treatment at 1.6 mg/m²/day. At higher doses of ZD9331, more constant elevations were seen. At doses of 6–8 mg/m²/day, plasma dUrd levels rose rapidly and remained elevated for up to 2 weeks (Fig. 4).

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during ≥5 cycles of treatment. These patients were treated at a variety of dose levels from 0.125 to 8.0 mg/m²/day. Eight patients were not assessed for response because of a failure to receive ≥50% of the intended dose in ≥2 cycles. There was no relationship between ZD9331 dose and response.

DISCUSSION

This study evaluated a 5-day continuous i.v. infusion of ZD9331 in patients with refractory solid malignancies. Using this regimen, we found that toxicity was acceptable and manageable. The DLT was mainly hematological: 3 of the 6 patients treated at 8 mg/m²/day had grade 4 thrombocytopenia, 1 had grade 4 neutropenia, and 2 had grade 3 neutropenia. Reversible asymptomatic elevation of liver transaminases was seen across most dose levels, as was nausea and vomiting, which was rarely severe. Diarrhea was seen at the highest dose levels, but grade 4 diarrhea only occurred in 1 patient with significant hematological toxicity. Stomatitis and a self-limiting erythematous, pruritic, macular rash became more frequent at higher dose levels.

On the basis of an assessment of toxicities seen during dose escalation, a MTD of 6.0 mg/m²/day was identified; however, a continuous infusion was not felt to be necessary for therapeutic efficacy. Two other Phase I studies, started after the preliminary pharmacokinetic data from this study became available, in which ZD9331 was given as a 30-min infusion either on day 1 or on days 1 and 8 of a 3-week cycle, have now been completed (11, 12). The recommended i.v. dose of ZD9331 for Phase II studies is 130 mg/m² on days 1 and 8, repeated every 3 weeks. This current infusional study was continued after the demonstration of a long elimination t½, as it was felt possible that intermittent dosing may have resulted in a different toxicity profile.

We found that ZD9331 had nonlinear pharmacokinetics as mean CL increased ~3-fold over the dose range investigated. The renal route was found to contribute significantly to the clearance of ZD9331 in humans, accounting for ~40% of the mean total clearance (at a dose of 6 mg/m²/day). Calculated CLR values exceeded the estimated filtration clearance of ZD9331 in the kidney, which is known to be low because of the high (98%) plasma protein binding of ZD9331 (1). This would suggest that active tubular secretion of ZD9331 contributes to the renal elimination of ZD9331. Saturation of renal distal tubular reabsorption is one possible explanation for the dose-related changes in clearance and the long elimination t½ in humans.

Treatment with TS inhibitors results in an increase in plasma dUrd levels and, thus, plasma dUrd may be a useful surrogate marker for drug activity, including duration of effect and dose threshold (13). Sustained increases in plasma dUrd levels were seen in this study at the higher doses of ZD9331, suggestive of prolonged TS inhibition as a result of slow CL. The clinical usefulness of plasma dUrd levels as an indicator of both the efficacy and toxicity of ZD9331 is being investigated during other studies in the clinical trial program.

Of the 37 patients evaluable for response, 2 patients had a partial response, 10 patients had stable disease, 4 of whom had stable disease during ≥5 cycles of treatment. Additional evidence of antitumor activity may have been seen if more patients had been treated at a therapeutic dose.

Two Phase I studies have evaluated different oral regimens of ZD9331 (14, 15). Phase I combination studies have also been performed with cisplatin (16), topotecan (17), and gemcitabine (18). Combinations generally appear feasible; the doses of both drugs used in the topotecan combination were limited by myelosuppression and in the case of gemcitabine by a variety of side effects. However, ZD9331 at 130 mg/m² i.v. on days 1 and 8, i.e., the single agent Phase II dose for this regimen, could be administered with cisplatin 50 mg/m² i.v. on a 3-week schedule, a combination well worth exploring in the appropriate tumor types (16).

Phase II clinical studies of ZD9331 as a 30-min infusion on days 1 and 8 of a 3-week cycle have now commenced in patients with a range of tumors. Good response rates have been achieved, for example, in patients with advanced colorectal cancer: 73% of those failing first-line therapy had stable disease.

Fig. 4  Mean percentage changes in plasma dUrd over the course of cycle 1 for the 6 mg/m²/day (n = 6) and 8 mg/m²/day (n = 6) dose groups.
on ZD9331, whereas >50% of patients receiving ZD9331 as third-line therapy had a partial response (4.5%) or stable disease (47.7%; Ref. 19). Also, in a study in heavily pretreated ovarian cancer patients, 9 of 44 (20.5%) had a complete response, partial response, or stable disease on ZD9331 (20) A comparison with gemcitabine in the treatment of advanced pancreatic cancer was reported as showing increased median survival (152 versus 109 days) and time to progression (70 versus 58 days) in those treated with ZD9331 with more ZD9331 patients alive at the end of study (21). Nevertheless, there were some concerns about toxicity, especially myelosuppression. The results of all of the studies to date show that ZD9331 is generally well tolerated, with a different toxicity profile from that of antimetabolites that require polyglutamation, such as raltitrexed and pemetrexed. DLT is hematological, predominantly thrombocytopenia, and nonhematological toxicities, especially mucositis and diarrhea, are mild. ZD9331 may be a useful drug in those patients with resistance to other antimetabolites and may have a different spectrum of activity.

REFERENCES
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