A phase I and pharmacokinetic study of the nonpolyglutamatable thymidylate synthase inhibitor ZD9331 plus docetaxel in patients with advanced solid malignancies

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Summary

Purpose: To assess the feasibility of administering ZD9331, a thymidylate synthase (TS) inhibitor that does not undergo polyglutamation and has broad antitumor activity, in combination with docetaxel in patients with advanced solid malignancies. The study also sought to determine the principal toxicities of the regimen and recommend appropriate doses for phase II studies, characterize the pharmacokinetics of the agents, evaluate the possibility of major drug-drug interactions, and seek preliminary evidence of anti-cancer activity. Patients and methods: Patients with advanced solid malignancies were treated with escalating doses of docetaxel as a 60-minute intravenous (IV) infusion followed 30 minutes later by ZD9331 as a 30-minute IV infusion every 3 weeks. At least three patients were treated at each dose level, and the maximum tolerated dose level was defined as the highest dose level that was not associated with an unacceptably high incidence of severe toxicity. The pharmacokinetics of both ZD9331 and docetaxel were also characterized. Results: Nineteen patients were treated with 71 cycles of ZD9331 and docetaxel (ZD9331/docetaxel) at dose levels that encompassed dosing iterations of ZD9331 ranging from 65 to 260 mg/m² and docetaxel doses in the range of 50 to 75 mg/m². Neutropenia was the principal toxicity of the ZD9331/docetaxel regimen. Since five of six patients treated at the ZD9331/docetaxel dose-level of 260/60 mg/m² had grade 4 neutropenia that was brief and uncomplicated in the first course, a rigorous exploration of higher dose levels was not undertaken. Nonhematologic toxicities, consisting of malaise, diarrhea, rash, nausea, and vomiting, were also observed, but these effects were rarely severe. No major antitumor responses were observed. The pharmacokinetics of both ZD9331 and docetaxel were similar to those reported in previous studies of each agent administered alone, suggesting the lack of major drug-drug interactions. Conclusion: The combination regimen, consisting of ZD9331 and docetaxel, is feasible and well tolerated at single-agent doses that are clinically-relevant. This ZD9331/docetaxel regimen does not appear to be associated with either major pharmacokinetic or toxicologic drug-drug interactions. A ZD9331/docetaxel dose level of 260/60 mg/m² is recommended as an initial dose level in disease-directed studies of the regimen, with further dose escalation of docetaxel to 75 mg/m² if the initial treatment is well tolerated. Further studies with this regimen are warranted in tumor types that have demonstrated sensitivity to both agents.

Introduction

Thymidylate synthase (TS) catalyzes the methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (TMP), an essential precursor for DNA synthesis [1–4]. Since thymidine nucleotides are used exclusively for DNA synthesis and malignant cells generally have higher proliferative rates and TS expression...
than normal cells, and also depend on *de novo* pyrimidine biosynthesis to a much greater degree, TS is a logical strategic for therapeutic development against cancer [1–4]. Indeed, several folate-based TS inhibitors have demonstrated notable clinical activity, but several mechanisms of intrinsic and acquired resistance have limited the magnitude, scope, and durability of their anticancer activities [1–4]. These resistance mechanisms include diminished cellular uptake by the saturable reduced-folate carrier (RFC) and impaired intracellular formation and/or retention of drug polyglutamates due to alterations in the expression of folylpolyglutamate synthetase (FPGS) and/or high folylpolyglutamyl hydrolase (FPGH) activity [1–9]. Furthermore, the formation and retention of polyglutamates in tissues with high FPGS activity such as liver and bone marrow may contribute to many of the sporadic toxicities observed with polyglutamatable TS inhibitors and other antifolates [5–9].

ZD9331 ((S)-2-[4-[N-(3,4-dihydro-2,7-dimethylquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido]-4-(1H-1,2,3,4-tetrazol-5-yl)-butyric acid; Figure 1), a water soluble, quinazoline, antifolate inhibitor of TS, was synthesized to avoid inherent drug resistance and circumvent acquired drug resistance caused by alterations in FPGS expression or high FPGH activity [1–4, 10–14]. Unlike many other TS inhibitors, such as raltitrexed (Tomudex\textsuperscript{TM}; AstraZeneca, Ardeley Park, United Kingdom), ZD9331 is not a substrate for FPGS, however, both antifolates are transported into the cell by the RFC [10–21]. ZD9331 is a potent inhibitor of both TS (Ki ≈ 0.4 nM) and tumor cell proliferation (IC\textsubscript{50} values for a range of human tumor cell lines ≈ 5–100 nM) [14]. Although polyglutamation serves to augment the retention of toxic species within cells, the cellular efflux of ZD9331 is not impaired in this manner and, instead, TS inhibition is rapidly reversed when tumor cells are resuspended in drug-free media [12, 14]. ZD9331 demonstrated impressive and broad activity against human tumor xenografts of colon (LoVo, Colo-205, HT-29), lung (HX147, N592, N417A), ovary (HX62), and gastric (MKN45) origin [10–14, 22]. In animal toxicology studies, rapidly proliferative tissues, including hematopoietic and gastrointestinal tissues, were most prone to the toxic effects of ZD9331 [12].

Early clinical evaluations were conducted with ZD9331 on a variety of schedules including a 30-minute IV infusion every 3 weeks, daily × 5 every 3 weeks, and weekly × 2 every 3 weeks, and a 5-day continuous IV infusion [23–26]. Myelosuppression was the principal toxicity of the agent on all schedules. The rationale for evaluations of ZD9331 as a protracted infusion and on divided dosing schedules was based on preclinical pharmacologic studies that demonstrated rapid clearance in both mice and dogs, but drug clearance in humans was very slow (t\textsubscript{1/2} ≈ 75 hours). Plasma concentrations of deoxyuridine (dUrd), a biochemical surrogate of TS inhibition, increased markedly following treatment on all schedules. For example, plasma dUrd concentrations increased 300%, with maximal levels on days 2 to 3 after treatment with 130 mg/m\textsuperscript{2} of ZD9331 [27]. Further disease-directed studies were principally conducted with ZD9331 administered as a 30-minute IV infusion weekly × 2 every 3 weeks at its maximum tolerated dose (MTD),

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**Figure 1.** Chemical structure of ZD9331, demonstrating pertinent functional elements of the agent.