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Phase II Open Label Study of the oral VEGF-Receptor inhibitor PTK787/ZK222584 (Vatalanib) in Adult Patients with Refractory or Relapsed Diffuse Large B Cell Lymphoma

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Abstract

PTK787/ZK222584 (Vatalanib), an orally active inhibitor of vascular endothelial growth factor receptors (VEGF-Rs), was evaluated in this phase II study of 20 patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Patients received once daily PTK787/ZK222584 at a target dose of 1250mg. Eighteen patients were evaluable for response: 1 patient had a complete response (CR), 6 patients had stable disease but subsequently progressed, 10 patients had progressive disease by 3 cycles, and 1 subject withdrew before response evaluation. The patient who attained a CR underwent autologous stem cell transplantation and remains disease free 76 months after study completion. There were no grade 4 toxicities. Grade 3 thrombocytopenia occurred in 20% and grade 3 hypertension occurred in 10%. There were no episodes of grade 3 proteinuria. In conclusion, PTK787/ZK222584 was well tolerated in a heavily pretreated population of DLBCL patients, though its therapeutic potential as a single agent in DLBCL appears limited.

Keywords

PTK787/ZK222584; Vatalanib; angiogenesis; Diffuse Large B Cell Lymphoma

INTRODUCTION

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common Non Hodgkin Lymphoma (NHL) subtype in the United States and Europe. [1, 2] Combination chemo-immunotherapy incorporating an anthracycline, such as cyclophosphamide, doxorubicin, vincristine, and prednisone and rituximab (R-CHOP) has been the standard, providing durable complete

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responses of 75–85%. [3–8] Despite these advances, only approximately 2/3 of DLBCL patients treated with such regimens will be alive and lymphoma free at a median of 4 years, and greater than one third progress after first line therapy. [9, 10] While autologous bone marrow transplantation (ABMT) helps some, a significant number of patients are not candidates for this approach or subsequently relapse. [4] In summary, there is a substantial population of patients with relapsed or refractory DLBCL in need of novel therapeutic options.

Angiogenesis, the process in which endothelial cells of established vasculature are stimulated to proliferate and migrate to form new blood vessels, is an attractive anti-neoplastic target given the dependence on a constant blood supply for tumor persistence, growth and metastasis. [11,12] We and others have shown the relevance of this process in hematologic malignancies. For example, bone marrow vascularity is increased in acute and chronic leukemias, myeloproliferative disorders, and multiple myeloma, and increased measures of angiogenesis are correlated with adverse prognosis. [13–16] Similar findings were confirmed in the NHLs, where levels of important pro-angiogenic growth factors such as VEGF, basic-fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and angiogenin were higher in affected patients compared to unaffected individuals. [17,18] These angiogenic factors in NHLs also correlate directly to markers of survival and response to therapy. [17, 19–21]

PTK787/ZK222584, an orally active amino-phthalazin, is a potent angiogenesis inhibitor which blocks all known tyrosine kinase receptors of VEGF including VEGFR1 (Flt-1), VEGFR2 (KDR) and VEGFR3 (Flt-4). [22, 23] Several clinical studies established the safety and efficacy of PTK787/ZK 222584 in various solid malignancies as well as in hematologic disorders such as acute myeloid leukemia, myelodysplastic syndrome, and multiple myeloma. [24–27] This reports a phase 2 efficacy study of PTK787/ZK222584 in patients with refractory and/or relapsed diffuse large B-cell lymphoma.

METHODS

Patient Eligibility

Patients with measurable relapsed or refractory DLBCL (*de novo* or transformed) were eligible. Additional key criteria for inclusion were Karnofsky Performance Score (KPS) 70, normal renal and liver function, and hematologic parameters defined as hemoglobin (Hgb) 9 g/dL, Absolute Neutrophil Count (ANC) $1.5 \times 10^9/L$ ($1500/mm^3$), and platelets (PLT) $100 \times 10^9/L$ ($100,000/mm^3$) unless due to bone marrow involvement. Central nervous system disease, prior allogeneic transplant, uncontrolled hypertension, proteinuria, or previous anti-VEGF therapy excluded subjects from enrollment. The study was approved by the Institutional Review Boards (IRB) at all participating institutions and was registered on www.clinicaltrials.gov, identifier NCT00511043. All subjects signed informed consent.

Study Design

This was a phase II open label study to assess efficacy and safety of PTK787/ZK222584 in relapsed/refractory DLBCL. It was initially estimated that 42 patients would be accrued to

this trial with 15% expected to be unevaluable for response due to withdrawal within the first 4 weeks. Based on this projection, a maximum of 35 evaluable patients would be accrued using a two-stage admissible design that allows the trial to stop early for lack of efficacy. [28] The null hypothesis that the probability of a response (CR+PR) is less than or equal to 0.05 was planned to be tested against the alternative hypothesis that the response rate is greater than or equal to 0.20. Due to poor accrual, the study was closed early after 20 patients had enrolled.

All patients initiated PTK787/ZK222584 at a dose of 750mg by mouth (PO) daily on days 1–28 of a 28 day cycle. Drug dose was increased weekly, initially to a dose of 1000mg PO daily and then to a target dose of 1250mg daily unless a grade 2 toxicity developed. Patients remained on continuous dosing for up to 12 cycles unless they had unacceptable toxicities, disease progression, or withdrawal from study. Up to three dose reductions were allowed for toxicities.

The primary endpoint was overall response rate (complete response (CR) + partial response (PR)). Only subjects who received study drug for at least 4 weeks were considered evaluable for response (unless they progressed within 4 weeks as the reason to discontinue early).

Response was determined initially by standard criteria for NHL described by Cheson et al. and current at the time of study start-up, and reassessed by updated guidelines that incorporate PET imaging in determining response. [29,30]

Secondary endpoints included safety and tolerability. All subjects who received at least one dose of study drug were evaluable for safety. Adverse events were graded using the National Cancer Institute (NCI) Common Toxicity Criteria (CTCAE) in force during the conduct of the study (version 3.0).

RESULTS

Enrollment and Patient Baseline Characteristics

Twenty patients (11 female) with a median age of 61 years (range 31–85 years) were enrolled between November 2005 and July 2008. All twenty patients (100%) had received at least one prior rituximab containing regimen, and 60% had received three or more prior therapies. Five (25%) of patients had prior autologous stem cell transplantation. Three patients (15%) had transformed to DLBCL from an indolent lymphoma and 4 patients (20%) had been characterized as “T-cell rich” DLBCL.

Toxicities and Tolerability

Overall PTK was well tolerated with no grade 4 adverse events. Thrombocytopenia was the most frequent grade 3 toxicity, occurring in 20% of patients. All other grade 3 toxicities occurred in <10% of patients. Thrombotic events have been seen in subjects receiving VEGF inhibitors and one subject was diagnosed with a lower extremity DVT at study completion. There were no noted gastrointestinal perforations. Other common grade 1/2 toxicities occurring in greater than 15% of patients are described in Table I.

Cardiac dysfunction, hypertension, and proteinuria have all been reported in patients receiving VEGF-inhibitors. In this study, HTN and proteinuria, of any grade, each occurred in 25% of patients. Although there were no episodes of grade 3 proteinuria, grade 3 hypertension (HTN) occurred in 10% but resolved with additional oral medications. Two patients were found to have grade 3 left ventricular dysfunction/congestive heart failure (CHF) while on this study. The first patient had a persistent cough and an echocardiogram revealed an EF of 25–35% with moderate improvement but persistence of global hypokinesis 4 months later. This patient had received multiple prior treatment regimens including an anthracycline, but had no evidence of coronary artery disease on cardiac catheterization. A baseline echocardiogram was not required immediate prior to enrollment to definitively determine whether cardiac function worsened while on study drug, though a TTE 10 months prior to study start was reportedly normal in this patient. The second patient, who had only received 3 cycles of study drug, was incidentally found to have a depressed EF of 37% on echocardiogram performed 2 months after stopping study drug.

Eighteen of the 20 patients enrolled escalated to the full target dose of 1250mg, but 6 required at least 1 dose reduction due to adverse events (sepsis, vertigo, transaminitis, rash or fatigue). One patient required two dose reductions given refractory fatigue and nausea. Patients received a median of 3 cycles of PTK787/ZK222584 (range 0–6). Three patients were withdrawn from study because of adverse events: one patient with sepsis, and one patient had altered mental status despite dose reductions. A third patient who had stable disease at 3 cycles of therapy stopped study drug due to persistent grade 3 AST elevations despite dose modifications.

Responses

Eighteen patients received study drug for at least one cycle and were technically considered evaluable for response; however, one patient withdrew early due to toxicity and was not fully restaged. Of the remaining 17 patients, ten patients had progressive disease (PD) by 3 cycles of therapy. Six patients initially had stable disease after 3 cycles of treatment but five of these patients had PD when reassessed after 6 cycles and one withdrew after 2 cycles to pursue other therapeutic options. One patient achieved a CR with PTK787/ZK222584 after 3 cycles. This patient had primary refractory DLBCL to R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone) and RICE (rituximab, ifosfamide, carboplatin, etoposide). The patient subsequently received two additional cycles of PTK787/ZK222584 (for a total of 5 cycles) and underwent autologous stem cell transplantation one month later. At most recent followup assessment 76 months after study completion, the patient was alive and without evidence of disease.

Discussion

PTK787/ZK222584 is an orally active VEGF inhibitor which was well tolerated in a heavily pretreated population of patients with DLBCL. In this Phase II study of twenty patients, there were no grade 4 toxicities. Though proteinuria, uncontrolled hypertension, and cardiac dysfunction have occurred with the use of VEGF inhibitors, there were no episodes of grade 3 proteinuria in this study and grade 3 hypertension only occurred in 10% of patients. The

two patients found to have grade 3 CHF while on study have insufficient evidence to definitively attribute the cardiac dysfunction to the study drug.

Despite the general tolerability of PTK787/ZK222584, its therapeutic potential as a single agent given as a daily dose in the aggressive lymphoid malignancies appears limited. However, durable stable disease with a well-tolerated oral agent in such a population, as noted here with 7 out of 20 patients, may be encouraging in some circumstances or provide an attractive agent for synergy with other compounds. Additionally, one patient did achieve a CR, remaining disease free for over 6 years after autologous stem cell transplant. This excellent response in a single patient raises the possibility that a subset of patients may derive significant benefit from PTK787/ZK222584. Unfortunately, there were no obvious distinctive factors of this patient's disease or clinical course to suggest why they responded when other patients did not, and the numbers in this study were too small to develop a model predictive of response.

Several explanations for the low observed response rates in this study are hypothesized. First, there may have been inadequate dosing of PTK787/ZK222584. Subjects in this study received once daily dosing which was the accepted standard regimen at the time the trial was open. However, subsequent data from trials of PTK787/ZK222584 in advanced malignancies demonstrated twice daily dosing (BID) had significantly better clinical results. Correlative pharmacokinetic studies in these trials found higher trough drug levels in the patients receiving the study drug BID, providing a plausible explanation for the improved outcomes. [31, 32] Despite these results, testing of increased dose of PTK787/ZK222584 in relapsed/refractory DLBCL patients is unlikely to be undertaken given low response rates seen thus far and concerns of increased toxicities with higher doses.

Alternatively, the results of this and similar studies suggest that the disappointingly low responses may be due to the ineffectiveness of VEGF or VEGF-R inhibitors as a class in the treatment of aggressive lymphomas rather than to the specific activity of PTK787/ZK222584. In the phase II SWOG-0108 study of 45 patients with aggressive lymphomas (30 with DLBCL) utilizing an alternate single agent VEGF inhibitor, bevacizumab, an even lower response rate was observed than in our study with only one patient demonstrating a partial response. [33] Sunitinib, a multi-targeted VEGF-R inhibitor, has also been tested in relapsed/refractory DLBCL and similarly no objective responses were seen in the 15 evaluable patients. [34]

Finally, we considered that angiogenesis, or at least the VEGF target, may not be a dominant factor in the pathogenesis of aggressive lymphomas to make them an effective single agent drug. In this case, however, VEGF inhibitors as part of a multi-drug regimen with traditional cytotoxic chemotherapy may still lead to superior results. Though combinations of PTK787/ZK222584 with established cytotoxic regimens have not yet been clinically investigated in DLBCL, the results of the phase II SWOG 0515 frontline study adding the anti-angiogenesis agent, bevacizumab, to R-CHOP were recently published. Unfortunately, in the 64 eligible patients on this study, not only did the combination with bevacizumab fail to demonstrate a therapeutic improvement, but there were significant additional cardiac and gastrointestinal toxicities in the bevacizumab combination regimen. [35] Additionally, the large randomized

multicenter placebo controlled phase III MAIN study adding bevacizumab to standard R-CHOP therapy failed to demonstrate improved outcomes with the addition of bevacizumab and recruitment was stopped early due to suppression of left heart function and increased incidence of symptomatic CHF. [36]

As knowledge of the critically needed pathway blocks for effective interruptions in angiogenesis grows, the efficacy of anti-angiogenesis agents in lymphoma may drive further investigation for rational combinatory regimens incorporating other novel targeted small molecule inhibitors. However, the increased complications when combined with traditional cytotoxic regimens, and their minimal single agent anti-lymphoma activity, create an uncertain future for VEGF inhibitors in the treatment of aggressive lymphomas.

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Table I

Toxicities

Adverse Event*	No. patients (%) with grade 3 toxicity**	No. patients (%) with toxicity across grades
Blood/Bone Marrow		
anemia	0	7 (35)
thrombocytopenia	4 (20)	5 (25)
Cardiac		
prolonged QTc	1 (5)	3 (15)
hypertension	2 (10)	5 (25)
Ventricular dysfunction	2 (10)	2 (10)
Constitutional		
fatigue	2 (10)	13 (65)
fever, non-neutropenic	0	4 (20)
Gastrointestinal		
anorexia	1 (5)	9 (45)
constipation	0	4 (20)
dehydration	2 (10)	2 (10)
diarrhea	0	5 (25)
nausea	2 (10)	15 (75)
vomiting	1 (5)	7 (35)
Other		
proteinuria	0	5 (25)
dizziness	1 (5)	4 (20)

* Grade 3 adverse events reported for all patients (n=20). Grade 1/2 events reported for those occurring in greater than 15% of patients.

** There were no grade 4 toxicities in this study.