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Feasibility of administering oblimersen (G3139; Genasense) with imatinib mesylate in patients with imatinib resistant chronic myeloid leukemia – Cancer and leukemia group B study 10107

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Abstract

The CALGB studied the feasibility and effectiveness of adding oblimersen (G3139; Genasense) to imatinib mesylate (IM) in imatinib-resistant chronic phase chronic myeloid leukemia (CML) patients. We hypothesised that IM resistant CML cells are no longer being driven to proliferate by Bcr/Abl activity alone. Instead, the anti-apoptotic protein Bcl-2 would regulate one of the pathways controlling growth and/or viability. Thus, blocking both Bcr/Abl and Bcl-2 simultaneously would result in hematologic and cytogenetic improvement. Oblimersen was administered via continuous intravenous infusion over 10 days every 21 days, along with daily IM. Doses of both drugs were escalated in 3 cohorts; the initial dose of IM was 600 mg/day. Response was defined as a decrease by > 30% in the percentage of t(9;22) metaphase cells. Twelve patients had primary and nine had secondary imatinib resistance. Ten patients received 4 mg/kg/day oblimersen/600 mg IM, six patients received 7 mg/kg/day oblimersen/600 mg IM and five patients received 7 mg/kg/day oblimersen/800 mg IM. Only two (9.5%) patients achieved a decrease by > 30% in the percentage of t(9;22) metaphase cells. Although the combination of oblimersen and IM is safe and feasible, we did not observe clinical benefit in these patients with imatinib-resistant CML using these doses and schedule.

Keywords

Chronic myeloid leukemia; imatinib mesylate; resistance; oblimersen; bcl-2

Introduction

Imatinib mesylate (IM) is a potent and relatively specific inhibitor of the Bcr/Abl tyrosine kinase. Most patients with chronic myeloid leukemia (CML) have shown rapid hematologic, cytogenetic and molecular responses to IM therapy [1]. In a phase II study (Novartis 110) involving 532 patients with chronic phase CML refractory or intolerant to interferon α , the median times to achieve hematologic and cytogenetic responses were 0.7 and 3 months, respectively [2]. Those who did not achieve complete hematologic response (CHR) after 8 weeks or did not achieve a partial cytogenetic response (PCyR) after 3 months had a higher rate of disease progression. Such patients may benefit from other treatment approaches.

In the phase III randomised trial of IM versus interferon α and cytarabine in newly diagnosed chronic phase CML patients (Novartis 106), a substantial number of patients who did not achieve complete cytogenetic remission at 6 months went on to achieve complete cytogenetic remission at 12 months [1]. These data suggested that one should wait at least 12 months prior to offering additional treatment options to patients without complete cytogenetic remissions. However, if one looks at the data from the phase II trial [2], those patients who did not achieve complete cytogenetic remission after 3 months of IM had a higher risk of disease progression. The randomised study included a more favourable patient population, that is, previously untreated patients who had not failed other therapies. Therefore, we proposed to offer additional treatment interventions to patients who achieved neither complete hematologic remission following 8 weeks nor complete cytogenetic remission following 6 months of IM.

Various mechanisms of resistance to IM have already been described [3,4]. On the basis of these data, simultaneous interruption of two signal transduction pathways may represent one effective anti-leukemic strategy [5]. One of the downstream targets of Bcr/Abl phosphorylation is the anti-apoptotic protein, Bcl-2. It is likely that Bcl-2 acts in concert with other related proteins to regulate the pathway leading to apoptosis [6].

Inhibition of Bcl-2 has recently been attempted through a variety of strategies including anti-sense strategies, which directly diminish the amount of this protein. Indeed, pre-clinical data demonstrated that one such compound, oblimersen, an 18-mer phosphorothioate oligodeoxynucleotide (5'-TCTCC CAGCGTGCGCCAT-3') designed to bind to the first six codons of the human *BCL-2* mRNA, induced marked apoptosis of imatinib-resistant CML cell lines [7]. Further, nude mice transplanted with imatinib-resistant Bcr-Abl transformed cells and treated with oblimersen showed longer survival when compared with untreated mice or those treated with IM alone [7]. Tumor samples examined after 5 days of oblimersen treatment had decreased Bcl-2 expression. Finally, cells harvested from oblimersen-treated animals were more sensitive to subsequent treatment with IM. These data suggested that the combination of oblimersen and IM may be useful in circumventing clinically acquired resistance to IM.

Materials and methods

Patients

Patients were eligible if they had CML in chronic phase. They must have received prior therapy with IM at 400 mg/day for > 8 weeks without CHR or for > 6 months without a PCyR, and must not have evidence of progressive disease (accelerated or blastic phases). In addition, eligible patients must have received a stable dose of imatinib of 600 mg/day for at least 4 weeks without > grade 1 toxicity. Primary resistance was defined as CML that never achieved either a hematologic or cytogenetic response. Secondary resistance was defined as loss of a previously achieved hematologic or cytogenetic response. Patient registration and data collection were managed by the CALGB Statistical Centre. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The protocol was reviewed and approved by the institutional review board at each trial centre.

Treatment protocol

Oblimersen was administered to outpatients via continuous intravenous infusion with an ambulatory pump over 10 days and repeated every 21 days, along with daily oral IM. Doses of both drugs were escalated in 3 cohorts (Table I) to ensure safety. Patients were treated with the combination for a maximum of 4 cycles of therapy.

Response criteria

CHR was defined as the disappearance of all signs and symptoms of the disease including palpable splenomegaly. The white blood cell (WBC) and platelet counts must fall within the institutional normal ranges. There could be no blasts or promyelocytes in the blood, and bone marrow differentials must have < 5% blasts. Cytogenetic response (centrally reviewed) required at least 20 bone marrow metaphase cells. Complete cytogenetic response (CCyR) was defined as no t(9;22) metaphase cells; PCyR was defined as 1–34% (9;22) metaphase cells; and minor cytogenetic response (MiCyR) was defined as 35–99% t(9;22) metaphase cells. Disease progression was defined as progression to either accelerated or blast phase, increase in the WBC count > 150% of the upper limit of normal (ULN) and/or the platelet count > 150% of ULN, or development of palpable splenomegaly. Cytogenetic progression was defined as an absolute increase > 30% in the percentage of t(9;22) metaphase cells.

Statistical analyses

The primary endpoint was cytogenetic response after two cycles of therapy. The secondary endpoints were hematologic, cytogenetic and molecular responses after two and four cycles of therapy, the duration of response, and the toxicities of the concomitant treatment with IM and oblimersen. Six institutions participated in the initial dose-escalation phase of the trial that was later opened to all CALGB institutions. A beneficial effect of the combination was defined as a decrease by > 30% in the percentage of t(9;22) metaphase cells in 20% of patients whose CML was resistant to IM alone. The planned sample size for the study was approximately 37 patients. A two-stage design was employed, testing the null hypothesis that the true response rate was 5% versus the alternative hypothesis that the true response

rate was 20%. Fisher's exact test [8] was used in an exploratory analysis of type of imatinib resistance (primary versus secondary) compared with best response to treatment. Data quality was ensured by careful review of the data by CALGB Statistical Centre staff and by the study chairperson. Statistical analyses were performed by CALGB Statisticians using the SAS version 9.1 and StatXact version 6 software packages.

Results

Patients

Patients were accrued between February 24, 2003 and March 23, 2005. The median age of the 21 enrolled patients (13 females and 8 males) who received any therapy was 54 years (range, 25–74), with 13 Caucasians and eight African Americans. Only 4 patients had been treated *de novo* with IM; all others had received other agents (hydroxyurea, interferon α , interferon α and cytarabine, homoharringtonine, others) prior to IM for a median of 22 months (range, 1–147). Twelve patients had primary and 9 had secondary IM resistance. Six patients had never achieved CHR. Only 2 patients had previously achieved partial cytogenetic remission while on IM therapy. The median duration of IM treatment prior to enrolment on this trial was 30 months (range, 10–45) for the entire cohort with no apparent difference between patients with primary or secondary resistant CML (29 vs. 30 months).

Treatment

The first 10 patients received 4 mg/kg/day oblimersen and 600 mg of IM. The next 6 patients received 7 mg/kg/day oblimersen and 600 mg of IM, and the last 5 patients received 7 mg/kg/day oblimersen and 800 mg of IM. Grade 3 or 4 side effects possibly, probably, or definitely attributed to the combination are described in Table II. Toxicities exceeding 10% were fatigue (19%), neutropenia (38%), thrombocytopenia (24%) and febrile neutropenia (14%). There were no lethal events.

Response

Responses were seen in two of 12 (17%) patients with primary resistance as compared with four of nine (44%) patients with secondary resistance ($P = 0.18$; one-sided). The characteristics of the 6 responding patients are shown in Table III. Four patients (19%) achieved CHR, and 2 patients (10%) also had a complete or PCyR. One patient who initially achieved CHR on IM alone but lost it prior to study enrolment achieved CCyR on the combination of 7 mg/kg oblimersen and 600 mg of IM. Another patient who initially achieved cytogenetic response to IM alone but lost it prior to study entry achieved PCyR on the combination of 7 mg/kg oblimersen and 600 mg of IM. Because $< 10\%$ of patients (2/21; 95% confidence interval = 0.012, 0.304) had a decrease of $> 30\%$ in the percentage of t(9;22) metaphase cells, the study was terminated after 21 patients were enrolled.

Discussion

This clinical trial was conducted to evaluate the effect of oblimersen when added to IM in imatinib-resistant CML. Interestingly, the addition of oblimersen to fludarabine and cyclophosphamide has significantly increased the complete remission and nodular partial

remission rates as well as the response duration in patients with relapsed or refractory chronic lymphocytic leukemia [9]. Similarly, the addition of oblimersen to dacarbazine resulted in a significant increase in progression-free survival in patients with advanced melanoma [10]. However, oblimersen did not increase the CR rate or disease-free survival when added to daunorubicin and cytarabine in newly diagnosed patients with acute myeloid leukemia (AML) who were ≥ 60 years old [11].

Several reasons may explain the lack of a cytogenetic response by most of the patients (19/21) in our trial. One question relates to the uptake of oblimersen by the CML cells. Even though accumulation of oblimersen was demonstrated in AML blasts [12,13], the effect of concomitant IM on its uptake is unknown. However, in a phase II study of oblimersen and docetaxel in patients with hormone-refractory prostate cancer [14], where Bcl-2 protein levels decreased by approximately 50% in peripheral blood mononuclear cells after treatment, individual changes did not correlate with oblimersen steady state concentrations or response to therapy. Therefore, response does not always correlate with Bcl-2 down-regulation. Thus, we postulate that the lack of greater response in our trial was probably not related to lack of oblimersen accumulation within the CML cells.

Another possible explanation for low response rate may be the presence of *ABL* mutation(s) that interfere with imatinib binding. We did not evaluate our patient samples for the presence of *ABL* mutations. However, recent studies with dasatinib [15] and nilotinib [16] in imatinib-resistant chronic phase CML patients report mutations in about 40% of the patient samples, and our patient population would likely be quite similar. Therefore, our initial goal to detect a decrease of $> 30\%$ in the percentage of t(9;22) metaphase cells in $> 20\%$ of the patients could have been achieved even if 40% of the patient samples carried *ABL* mutations.

Finally, we designed our clinical trial based on preclinical data showing a beneficial effect for oblimersen in imatinib-resistant xenografts [7]. Bcl-2 levels are elevated in approximately 50% of CML patients [17] suggesting that the target was valid, but most probably the “weapon” was not sufficiently effective. A recent randomised study concluded that increasing the dose of IM was not as effective as switching to dasatinib [18]. However, the results obtained in that trial demonstrated only 30–40% CCyR following dasatinib therapy in imatinib-resistant CML, raising the potential to add oblimersen to dasatinib in a future clinical trial. The strategy of blocking two or more signalling pathways responsible for proliferation, apoptosis, or autophagy simultaneously merits further evaluation in imatinib-resistant CML.

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Table I

Treatment cohorts.

Treatment cohort	Oblimersen dose (mg/kg/day) [★]	Imatinib mesylate dose
1	4	600 mg/day
2	7	600 mg/day
3	7	400 mg twice daily

[★]Given by continuous intravenous infusion for 10 consecutive days.

Table IIImatinib mesylate and oblimersen combination-related toxicity events ($n = 21$).

	Grade 3	Grade 4
<i>Non-hematologic</i>		
Fatigue	3	1
Hyperbilirubinemia	1	0
Vomiting	1	0
Diarrhea	1	0
Headache	1	0
Syncope	1	0
Hypoxia	1	0
Hypophosphatemia	1	0
<i>Hematologic</i>		
Neutropenia	6	2
Lymphopenia	1	0
Thrombocytopenia	4	1
Anemia	1	0
Febrile neutropenia	3	0
Thrombosis	1	0

Table III

Characteristics of responding patients. ★

Patient No.	Prior other therapy (mo)	Prior imatinib therapy (mo)	Response to imatinib alone at study entry	Resistance	Cohort [†]	Number of courses	Best response	Duration of response (months)
1	10	26	No CHR	Primary	1	4	CHR	27.8+
2	12	30	No CHR	Secondary	2	4	CHR	6.5
3	1	37	No CHR	Secondary	2	4	CHR; CCyR	27.4+
4	4	45	CHR; No CyR	Secondary	2	4	CHR; PCyR	1.3
5	31	33	No CHR	Secondary	3	3	CHR	2.4
6	7	26	CHR; No CyR	Primary	3	3	CHR; MiCyR	0.3

★'Responding' refers to both hematologic and cytogenetic responses.

[†]Please refer to Table 1 for the details of each cohort.

Abbreviations: CCyR, complete cytogenetic remission; CHR, complete hematologic remission; CyR, complete hematologic remission; MiCyR, minor cytogenetic remission; PCyR, partial cytogenetic remission.