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Pegylated IFN-α2a combined to imatinib mesylate 600 mg daily can induce complete cytogenetic and molecular responses in a subset of chronic phase CML patients refractory to IFN alone or to imatinib 600 mg daily alone

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ABSTRACT

This phase I/II study was designed to demonstrate the tolerance and the efficacy of a combination of pegylated interferon-α 2a to Imatinib mesylate (IM) 600 mg daily in cytogenetically IM-resistant but in CHR chronic phase CML patients. The combination was generally well tolerated in the 15 evaluable patients. A significant reduction of the $Ph1^+$ BM metaphases was observed in these poor prognosis patients, with 2 long-term CCyR including 2 MMR. After a median follow-up of 43 months, 93% of patients are alive. The addition of PegIFNα2a to IM600 is feasible, and able to overcome resistance within this context.
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1. Introduction

The treatment of chronic myelogenous leukemia (CML) has been revolutionized by the introduction in the clinical arena in 1998 of therapies targeting the oncoprotein Bcr-Abl, which is sufficient to induce the disease by itself at initial stages. In early chronic phase, the vast majority of patients respond optimally [1,2] to imatinib mesylate (IM) 400 mg daily, however, in late chronic phase a substantial fraction (10–20%) of patients do not respond well and may represent a reservoir for overt resistance at molecular, cytogenetic or hematologic levels [3,4]. Despite the lack of specific knowledge on the mechanisms for IM-resistance, there is some evidence that escalating IM daily dose up to 800 mg may overcome hematological or cytogenetic resistance to conventional doses of IM [5] in chronic phase patients, but responses are not durable. Interferon is able to induce long-term disease control in chronic phase patients alone or in combination with cytarabine [6], particularly if a complete cytogenetic remission is obtained (10–20% of patients) [7,8]. Recently, the introduction of polyethylene glycol (pegylated) forms of interferon-α (IFN-α) in the treatment of CML, PegIFNα2a [9] and PegIFNα2b [10,11] have improved the tolerability of native IFN-α while maintaining [10] or improving [9] its efficacy. The

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precise mechanisms of activity of IFN-α remain partly obscure, but it is commonly recognized that it exerts some direct cytotoxic specific effects on Philadelphia positive ($Ph1^+$) leukemic cells and may enhance immune response(s) towards the tumour. Before the availability of second generation tyrosine kinase inhibitors (TKIs) in clinical trials, we designed and conducted a phase I/II trial of escalated doses of IM combined to PegIFNα2a for at least 1 year, in cytogenetically refractory patients to standard doses of IM and to escalated doses of IM for at least 3 months duration; speculating that the combination of both drugs with distinct molecular or cellular targets and different mechanisms of activity might be successful.

2. Material and methods

2.1. Patients

The AFR 10 trial has been approved by the local ethics committee [Comité sur la Protection des Personnes dans la Recherche Biomédicale (CPP)] Lyon B (Centre Léon Bérard, Lyon, France) and was conducted as a multisite study in centers of the French CML group (Fi-LMC group) between August 2004 and October 2005. All patients were enrolled after an informed consent form, approved by the ethicals committee, had been signed. All patients were over 18 years of age with a confirmed Philadelphia positive CML in chronic phase since diagnosis, with no allogeneic donor available. Additional requirements included a primary or secondary resistant CML to IM defined as the absence of major cytogenetic remission (MCyR) after a minimum of 1 year of IM and at least 3 months or more at ≥600 mg daily and still remaining in complete hematologic remission (CHR); and with an ECOG performans status ≤2.

2.2. Study design and treatment

This is a multicenter, open-label phase I/II study aiming to determine the safety and the efficacy of IM 600 mg daily combined to PegIFNα2a (Pegasys®, Roche SA, Neuilly, France) 90 μg once weekly for at least 12 months, unless adverse events require dosage reductions. Patients with a substantial benefit of this strategy were allowed to carry on the combination at the discretion of the investigator.

2.3. Dose modifications

Dose modifications were recommended if a first episode of grade 3 hematologic toxicity (according to the NCI classification) occurred, and both treatments were withheld until a grade ≤2 was obtained. Both treatments were restarted at the initial dosing. In case of a second episode of grade 3 hematologic toxicity or a first or second episode of grade 4 hematologic toxicity, both treatments were withheld and restarted until a grade ≤2 was obtained, at half dosing for both (i.e. IM 300 mg daily and PegIFNα2a 45 μg weekly). After that, if a new episode of grade 3 or 4 hematologic toxicity recurred, the patient was withheld from the study. The use of recombinant erythropoietin and/or G-CSF was allowed if necessary. For non-hematologic toxicity, the combination therapy was stopped in any case of grade 3 or 4 toxicities and restarted, for the first episode, at the initial dosing (for both drugs) until a grade ≤2 has been obtained and at half dosing (for both drugs) for the second episode and beyond.

2.4. Endpoints

The primary endpoint of this trial was to determine the rate of cytogenetic response (i.e. the % of Philadelphia positive bone marrow metaphases) and molecular response after 1 year of combined therapy with IM 600 daily and PegIFNα2a 90 μg weekly. Secondary endpoints were to explore the capacity of the combination therapy to maintain CHR, and to observe the hematologic and non-hematologic tolerances, and to analyze the overall survival.

2.5. Evaluation of patients

Patients were evaluated every 3 months for at least a year with clinical, routine biology tests (serum chemistry, creatinine levels, uricemia, LDH, liver enzymes), bone marrow aspirates with local karyotyping analysis, centralized peripheral blood reverse-transcriptase quantitative PCR (RQ-PCR) for BCR-ABL and BCR-ABL mutation screen in this cohort of patients at risk of developing such mutations (Laboratory for cytogenetics and molecular biology, centre hospitalier Lyon sud, Pierre Bénite, France) and centralized plasma VEGF level determinations (UMR6543, Université de Nice Sophia-Antipolis, Institute of developmental biology and cancer research, Nice, France). VEGF has been shown to be a surrogate marker for CML disease activity and response to IM [17] and we believe that it was important to assess plasma levels in this cohort of patients. Blood samples were shipped overnight to the reference laboratories. Karyotyping assessments were performed locally in each center according to standardized karyotyping techniques with at least 20 metaphases examined whenever possible. Responses were categorized according to the percentage of $Ph1^+$ metaphases observed: complete response (CCyR: no $Ph1^+$ metaphases detected), partial response (PCyR: 1–34% $Ph1^+$ metaphases), minor response (minor CyR: 35–64% $Ph1^+$), minimal (minimal CyR: 65–94% $Ph1^+$), and no response (95–100% $Ph1^+$). Reverse transcription and RQ-PCR to quantify BCR-ABL fusion transcripts and ABL control gene were performed according to the ELN recommendations [12,13], converted to the international scale (IS) [13] and expressed as a BCR-ABL/ABL ratio in percent. The BCR-ABL mutations were detected by direct sequencing (on both strands) from patients' peripheral blood samples as we described elsewhere [14]. VEGF plasma levels were performed by ELISA (Quantiquikine Human VEGF-A, R&D systems, Minneapolis, MN, USA) according to manufacturer's recommendations.

2.6. Statistical analysis

Survival analysis was based on the Kaplan–Meier method [15] and response duration was calculated from the initiation of the combination therapy until the latest follow-up. Whenever necessary, a 2-sided paired *t*-test was used to compare sets of data and a p value <0.05 was considered as statistically significant.

3. Results

3.1. Patients and treatment

Fifteen patients were treated in this study with a median age of 51 years (range 34–63 years) at diagnosis and of 56 years (range 40–69 years) at AFR 10 screening (Tables 1 and 2). Only 3 patients had low Sokal scores, whereas 8 were intermediate, 3 high (1 unknown), and 2 patients had a clonal evolution at diagnosis (Pt#9 and 14) illustrating the poor prognosis features of this cohort of patients at diagnosis. Most of the patients (10/15: 67%) were in late chronic phase and had IFN-α prior to IM for a median of 15.5 months (range 4–119 months) and all were resistant to IFN-α. Three patients (Pts#4, 5, 7) previously underwent G/GM-CSF mobilized, autologous stem cell transplantation for resistance to IFN-α (data not shown). IM was started at 400 mg daily for all after a median interval from diagnosis of 28 months (range 0.2–132 months). Ten patients experienced a cytogenetic response to IM (4 minor, 2 partial and 4 complete), but 5 had only a CHR with no cytogenetic response. All patients had increased doses to 600–800 mg daily of IM after a median of 11 months (range 4–46 months) because of primary (n = 5, Pts#6, 7, 8, 10, 12) or secondary (n = 10, Pts#1, 2, 3, 4, 9, 11, 13, 14, 15) cytogenetic resistance to IM standard doses, with no improvement after dose escalation.

At AFR 10 trial entry (Table 2), the patients showed poor prognostic features with a majority of patients with a minimal cytogenetic response or less (12/15, 80%). Moreover 8/15 patients (53%) with a clonal evolution in the $Ph1^+$ clone (Pts#3, 7, 8, 9, 11, 13, 14, 15), 6/15 patients (40%) harboured a BCR-ABL mutation (Pts#1, 2, 4, 5, 7, 10, with H396R, M244 V, M351T, H396R, L298V and D276G mutations, respectively), albeit all were in CHR [one (Pts#15) was considered as "near"-CHR as he had 8% myelocytes in the peripheral blood], as required by this trial criteria. All patients had peripheral blood BCR-ABL/ABL ratio above 2.5% and elevated VEGF plasma levels when compared to healthy donors (normal value 112 pg/ml) [17].

3.2. Efficacy

The evolution over time of the cytogenetic responses after combination therapy strategy initiation is shown in Fig. 1A and Table 3. The percentage of bone marrow $Ph1^+$ metaphases decreases slowly with time in a majority of patients, and 2 previously resistant patients to either therapy alone reached a CCyR status, and there was a trend towards statistical significance in the percentage of $Ph1^+$ metaphases observed between BM screening and month 12 assessments (p = 0.088). The BCR-ABL/ABL ratios (Fig. 1B and Table 3) followed a similar pattern with a slow but regular decline from screening (median: BCR-ABL/ABL ratio 26%, range 2.6–106.5) to month 12 (median: 12%, range 0.036–58.5), although not sta-

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