Imatinib mesylate in combination with chemotherapy in four children with *de novo* and advanced stage Philadelphia chromosome-positive acute lymphoblastic leukemia

The role of imatinib in childhood Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) has not been established. We treated four children with imatinib in combination with conventional chemotherapy (CT) before stem cell transplantation (SCT). Response evaluation consisted of fluorocytometric analysis of minimal residual disease (MRD) and standard qualitative RT-PCR follow-up.

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The Philadelphia chromosome is present in 2-4% of childhood ALL cases and represents an independent adverse prognostic factor, with 25-49% long term event free survival (EFS) rates.[1-4] Matched related donor stem cell transplantation (SCT) in first remission is considered the treatment of choice, with 65-83% EFS.[1,2,5,6] Alternative donor or autologous SCT did not prove to be superior to CT which, in turn, yields 30-40% EFS rates.[1,3,6] Factors such as low WBC at presentation, good initial steroid response, and response to induction CT after 8 and 15 days with four or three drugs respectively were correlated with outcome.[4,6] A slow, early response would identify patients with a lower remission rate and a poorer outcome.[7] Inversely, monitoring of MRD by RT-PCR and flow-cytometry would identify a subset of patients which might not need a SCT.[2,7,8] In fact, the poor prognosis of Ph+ALL was related to a slow response to induction.[1,7,9] Therefore, improving the quality of response during early treatment phases by introducing alternative agents such as imatinib, might improve treatment results. In adult Ph+ALL, this approach yielded excellent results.[10] Little information regarding the use of this drug in children has been reported. Imatinib has proved to be safe and effective in children with advanced Ph+ leukemia, raising questions as to its role as first line therapy before SCT.[5] One prospective randomized trial is currently evaluating the role of CT plus imatinib in the post-induction phase of children with Ph+ALL.[7] However, the low incidence of childhood Ph+ALL will probably preclude early evaluation in a randomized trial while evidence suggests that such an approach would probably improve outcome.

We analyzed our experience with imatinib in combination with CT before SCT in four children. Diagnostic features are summarized in Table 1. Imatinib was supplied on a compassionate basis after obtaining parental consent. Once started, imatinib was continued without interruption until transplantation. Bone marrow samples for morphology, flow-cytometry and RT-PCR were collected before starting combined therapy, and at 2-6 week intervals. Patient 1 started imatinib during the first week of induction. Patient 2 started imatinib fifty days after diagnosis, once intensification was completed. She was considered refractory because of a poor response to induction (70% leukemic cells by day +14 on flow-cytometry) and required mitoxantrone and high-dose cytarabine intensification to achieve hematologic remission (HR, <5% blasts on a bone marrow smear). Patients 3 and 4 started imatinib after first and second relapse respectively. They both achieved HR after one intensive BFM based CT course plus imatinib. Patients 1-3 received standard post-induction CT, while patient 4 continued intensive CT until transplantation. Fluorocytometric quantification of MRD and time to achieve molecular remission (MR, undetectable bcr/abl transcript by RT-PCR) were analyzed for response evaluation. Institutional Review Board approval was obtained for the analysis of results. Table 2 summarizes response and outcome. Median times to achieve <0.1% MRD and MR were 9 and 9.5 weeks respectively (range 2-16). Three patients achieved <0.01% MRD at a median time of 10 weeks (range 2-16). Patient 4 had a negative molecular result after six weeks but sixteen weeks were needed to achieve <0.1% MRD. These apparently contradictory results were related to the low test sensitivity for the b3a2 transcript detection. Hyperammonemic encephalopathy occurred in patient 3 after four months of combined therapy. It was related to L-asparraginase and recovery was noted six weeks after CT withdrawal while on imatinib monotherapy. Overt combined marrow and CNS relapse was diagnosed after 20 weeks on monotherapy. Interestingly, a new HR was achieved after one single BFM chemotherapy course in association with an escalated dose of imatinib (520 mg/m^2/day). The patient was then immediately scheduled to undergo SCT. CT withdrawal was necessary for patient 2 due to a disseminated fungal infection reactivation. Molecular relapse occurred 42 weeks later, but SCT was carried out in HR. Therefore, our series addressed concerns about emergence of imatinib resistance when used as monotherapy in advanced stage Ph+ALL.[7]

The four patients are alive in HR after a median time of 24 months from the introduction of imatinib (range 11-53)

Table 1. Patient characteristics.

Pt.	*Age[a] (yr)*	*Sex*	*WBC (×10^9/L)[a]*	*Leukemia phenotype[b]*	*CNS involvement*	*bcr/abl[b]*	*Prior therapy*
1	2	F	4.7	CD10+, CD19+, CD38+, μcyt+	No	e1a2	No prior therapy
2	8	F	61	CD10+, CD19+, CD38+, CD34+	No	e1a2	P, V, Dn, Cp, As, Ac, Mito, HDM, Mp, VM
3	7	M	197	CD10+, CD19+, CD33+, CD34+	No	e1a2	V, D, Dx, As, VP, Ac, Tg, P, Mp, M
4	8	M	220	CD10+, CD19+, CD34+, CD13+, CD33+	No	b3a2	Dx, Dn, V, As, Ac, VP, Tg, M, P, Mp, Cp, Ida, HDM

μcyt+: cytoplasm μ-chains positive; Ac: cytarabine; As: asparaginase; Cp: cyclophosphamide; D: doxorubicin; Dn: daunorubicin; Dx: dexamethasone; HDM: high dose methotrexate; Ida: idarubicine; Mito: mitoxantrone; M: methotrexate; Mp: mercaptopurine; P: prednisone; CNS: central nervous system; Tg: thioguanine; V: vincristine; VM: teniposide; VP: etoposide; [a]Data from patients 3 and 4 were provided by a referring institution. [b]Leukemia phenotype and bcr/abl molecular assay from patients 3 and 4 correspond to their first evaluation at our institution (first and second relapse respectively).

Table 2. Response to treatment and outcome.

Pt.	Disease status at enrollment	Marrow blasts (%)[a]	Imatinid dose ($mg/m^2/d$)	Concurrent CT	Time to < 1 % marrow blasts (weeks)[b]	Time to < 0.1 % marrow blasts (weeks)[b]	Time to molecular remission (weeks)[b]	Outcome	Donor (time to SCT in weeks[b])	Current status (follow-up time in months[b])
1	*De novo*	42	340	Standard induction and post-induction	2[c]	2[c]	2	HR and MR until SCT	MU (32)	Alive (18)
2	Ref[d]	0.13	340	Standard post-induction	0	14[c]	14	HR until SCT (molecular relapse after 42 weeks of imatinib monotherapy)	MR (68)	Alive (53)
3	1st relapse	12.5	260	Intensive BFM based followed by standard post-induction	4	4	16	Overt relapse after 20 weeks of imatinib monotherapy	MU (48)	Alive (14)
4	2nd relapse	10	300	Intensive BFM based	6	16[c]	6	HR until SCT	MU (30)	Alive (11)

CT: chemotherapy; HR: hematologic remission; MR: molecular remission; MR: matched related; MU, matched unrelated; Ref, refractory; SCT, stem cell transplantation. [a]Percentage of marrow elements with leukemic phenotype at fluorocytometric assay before starting combined therapy. [b]From the start of combined therapy. [c]< 0.01% MRD. [d]Poor response after 14 days of induction. [e]This patient achieved a new HR before STC.

and 28 months from diagnosis (range 18-54). In our view, these results represent a high success rate and contrast with previous data concerning CT alone. Coustan-Smith *et al.* found that Ph+ALL children failed to achieve <0.1% MRD after 19 days of induction, and most showed ≥1% leukemic cells at this point.[9] Cazzaniga *et al.* found that only 3 out of 27 children achieved a MR after 43 days of CT.[8]

Further evaluation of this approach is warranted in childhood Ph+ALL, particularly in patients lacking a suitable donor.

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