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Long-term follow-up of Philadelphia chromosome-positive (Ph^+) chronic myeloid leukaemia (CML) in children and adolescents managed at a single institution over a 20-year period

Chronic myeloid leukaemia (CML) rarely affects children. Allogeneic haematopoietic stem cell transplant (allo-HSCT) is feasible only for a minority of patients. Although clinical research on alpha-interferon (IFN) in CML began two decades ago, the few published series of childhood CML reported cytogenetic response (CyR) rates but no long-term treatment results (Dow *et al*, 1991; Millot *et al*, 2002). Recently, imatinib has shown efficacy in Philadelphia chromosome-positive (Ph^+) CML patients, also in those previously treated with IFN (O'Brien *et al*, 2003; Champagne *et al*, 2004; Kantarjian *et al*, 2004).

The treatment results, updated at December 2004, of 30 Ph^+ CML children and adolescents (16 males and 14 females; median age of 12·17 years), diagnosed at our Institution between June 1980 and September 2001, are reported (Table I). Allo-HSCT was performed in patients with a matched related donor (MRD), while those lacking a MRD received different treatments. Before 1989, patients without a MRD were treated with hydroxyurea; during that period, two patients underwent an autologous stem cell transplant (ASCT) and then low-dose IFN. Starting from 1990, 19 patients received IFN at a dosage of 2·5–9 MU/day (median 6 MU/day). When patients did not respond to IFN, a search was started for a human leucocyte antigen (HLA)-matched unrelated donor (MUD) and, from 1995, for umbilical cord blood (UCB) stem cells. Recently, patients who failed IFN were treated with imatinib.

A CyR was achieved in 11 of 17 evaluable patients treated with IFN (65%): complete (CCyR) in four and partial in seven; the median time to achieve maximal CyR was 12 months (range: 4–96 months). The CCyR persisted in three of the four complete responders, in whom the *BCR-ABL* transcript subsequently disappeared. Of the 14 patients who failed IFN treatment, five underwent allo-HSCT, while five were switched to imatinib and obtained a CCyR.

The projected 8-year survival of all patients treated with IFN was 63% [95% confidence interval (CI): 39·6–87·3]; censoring patients at the start of imatinib or at the date of allo-HSCT, the projected 8-year survival was 62% (95% CI: 31·6–92·7).

Thirteen patients underwent an allo-HSCT, seven of them had previously received IFN and one had also received an ASCT. Four patients that were allografted from a MRD are alive with no evidence of the *BCR-ABL* transcript, two of them after IFN dose escalation combined with a single donor lymphocyte infusion (DLI) because of disease recurrence.

Three MUD allografted patients and one patient submitted to a mismatched related donor transplant are alive with no evidence of the *BCR-ABL* transcript. The projected 8-year survival from the date of allo-HSCT for all transplanted patients, independent of the type of transplant, disease status, interval from diagnosis to transplant and prior therapy was 61% (95% CI: 33·5–87·7).

In our experience, which reflects the therapeutic changes that have occurred over the two last decades, the survival probability of patients treated with high-dose IFN is similar to that of patients submitted to allo-HSCT. The prolonged use of IFN did not impair the outcome of allo-HSCT and induced a CcyR, even after 8 years. Furthermore, it led to a *BCR-ABL* transcript disappearance in three of four CCy responders to high-dose IFN and in two children who had relapsed after transplant and subsequently treated with IFN combined with DLI. Disappearance of the *BCR-ABL* transcript after IFN has been recorded in adults, also in those who relapsed after allo-HSCT (Steegmann *et al*, 1999), but so far not in children. Furthermore, in agreement with reported data (Champagne *et al*, 2004; Kantarjian *et al*, 2004) imatinib induced CCyR in our children that had previously been treated with IFN.

In conclusion, our results indicate that IFN may still have a role in the future treatment strategies for childhood CML, combined or in sequential treatment with imatinib.

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Table I. Patients' characteristics at diagnosis and treatment results.

Patient number/sex	Age (years^{months})	Date of Diagnosis	ASCT	IFN	Time to IFN (months)*	Maximal CyR		IFN therapy		Other therapy	Allo-HSCT			Follow-up	Survival (months)*
						Ph$^+$ (%)	Time (months)	Suspended	Duration (months)		Type	Disease status	Interval* (months)		
1. M	$10^{5/12}$	06/27/1980	No	YES	113	N.E.		Yes	48	No	–	–	–	Death in CP (renal failure)	170
2. M	$7^{10/12}$	11/25/1982	YES	YES	N.E.	N.E.		N.E.		Allo-HSCT	MUD	A.P.	200	Death in 1st CCyR	202
3. F	$14^{11/12}$	07/01/1983	No	No	–	–	–	–		No	–	–	–	Death (BC)	6
4. F	$13^{6/12}$	12/19/1984	No	No	–	–	–	–		Allo-HSCT	MisRD	A.P.	19	Death (BC)	87
5. M	$13^{11/12}$	02/14/1986	YES	YES	N.E.	N.E.		N.E.		No	–	–	–	Death (BC)	152
6. M	$11^{5/12}$	02/26/1986	No	No	–	–	–	–		Allo-HSCT	MRD	First C.P.	3	Alive in second CCyR	+226
7. M	$14^{5/12}$	07/17/1986	No	Yes	34	100	–	Yes	65	Allo-HSCT	MisRD	A.P.	116	Alive in first CCyR	+221
8. M	$8^{9/12}$	02/01/1988	No	No	–	–	–	–		Allo-HSCT	MRD	First C.P.	3	Alive in first CCyR	+202
9. F	$1^{11/12}$	04/08/1988	No	No	–	–	–	–		No	–	–	–	Death (BC)	24
10. M	$13^{9/12}$	05/09/1990	No	Yes	1	100	–	Yes	46	No	–	–	–	Death (infection in BC)	52
11. M	$15^{10/12}$	02/05/1991	No	No	–	–	–	–		No	–	–	–	Death (infection in BC)	5
12. M	$7^{10/12}$	05/25/1991	No	Yes	2	94	9	Yes	11	No	–	–	–	Death (BC)	30
13. F	$9^{1/12}$	09/16/1992	No	Yes	4	0	96	No	+144	No	–	–	–	Alive in first CCyR	+148
14. F	$17^{1/12}$	03/06/1993	No	Yes	1	100	–	Yes	69	No	–	–	–	Death (BC)	72
15. F	$14^{4/12}$	10/19/1993	No	Yes	1	0	42	No	+133	No	–	–	–	Alive in first CCyR	+135
16. M	$15^{4/12}$	03/22/1994	No	Yes	1	100	–	Yes	10	Allo-HSCT	MUD	C.P.	12	Alive in first CCyR	+130
17. F	$9^{10/12}$	12/27/1994	No	No	–	–	–	–		Allo-HSCT	MRD	First C.P.	5	Alive in second CCyR	+121
18. F	$14^{9/12}$	10/15/1995	No	Yes	1	21	12	Yes	52	Allo-HSCT	MUD	First C.P.	63	Alive in first CCyR	+113
19. M	$15^{5/12}$	12/07/1995	No	Yes	4	80	30	Yes	50	Imatinib, CT, Allo-HSCT	UD-UCB	Aplasia	74	Death (TRM)	79
20. M	$6^{9/12}$	05/29/1996	No	Yes	6	N.E.		Yes	1	HU	–	–	–	Death (BC)	42
21. F	$5^{10/12}$	06/08/1996	No	Yes	1	90	4	Yes	7	Allo-HSCT	MUD	A.P.	18	Death (GVHD)	21
22. M	$11^{2/12}$	09/18/1996	No	Yes	4	83	12	Yes	14	Allo-HSCT	MUD	A.P.	18	Alive in first CCyR	+110
23. F	$9^{8/12}$	12/27/1996	No	No	–	–	–	–		Allo-HSCT	MRD	First C.P.	5	Alive in first CCyR	+99
24. F	$12^{5/12}$	12/02/1997	No	Yes	2	0	12	No	+81	No	–	–	–	Alive in first CCyR	+85
25. M	$12^{10/12}$	12/16/1997	No	No	–	–	–	–		Allo-HSCT	MRD	Second C.P.	6	Death (BC)	20
26. F	11	07/02/1998	No	Yes	2	100	–	Yes	39	Imatinib	–	–	–	Alive in first CCyR	+83
27. M	$17^{4/12}$	02/07/1999	No	Yes	2	54	6	Yes	18	Imatinib	–	–	–	Alive in first CCyR	+66
28. M	$9^{1/12}$	10/06/2000	No	Yes	4	0	18	Yes	26	Imatinib	–	–	–	Alive in first CCyR	+55
29. F	$17^{9/12}$	10/26/2000	No	Yes	1	100	–	Yes	8	Imatinib	–	–	–	Alive in first CCyR	+54
30. F	$10^{9/12}$	09/04/2001	No	Yes	5	50	12	Yes	12	Imatinib	–	–	–	Alive in first CCyR	+40

*From initial diagnosis.

ASCT, autologous stem cell transplantation; Allo-HSCT, allogeneic haematopoietic stem cell transplantation; N.E., not evaluable; MRD, matched related donor; GVHD, graft-*versus*-host disease; AP, accelerated phase; CP, chronic phase; CB, blast crisis; MUD, matched unrelated donor; CCyR, complete cytogenetic response; MisRD, mismatched related donor; CT, chemotherapy; UD-UCB, unrelated donor umbilical cord blood.

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