Discontinuation of imatinib in Belgian patients with chronic myeloid leukaemia

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On behalf of the MPN Belgian Hematological Society subcommittee

This article describes the Belgian register of chronic myeloid leukaemia patients who have stopped their treatment with imatinib in conditions comparable to the French STIM trial results: 44% remained in major molecular response off therapy; relapses appear rapidly after stopping imatinib and are responsive when the treatment is resumed.

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Introduction

Imatinib treatment dramatically improves survival in chronic myeloid leukaemia (CML) patients. The estimated overall survival of these patients was 85% at eight years (93% when deaths only related to CML were considered): with this therapy, the major molecular response ($MR^{4.5}$) at nine years is about 50%.[1] The reasons for stopping treatment can be due to medical (possible late toxicity or future pregnancy) or economic reasons. The pilot study on this subject, the STIM trial, shows that 41% of patients are staying in CMR twelve months after stopping their treatment.[2] These results were confirmed with longer follow-up.[3]

The results of the STIM trial probably convinced haematologists to suspend, with maintenance of monitoring, imatinib therapy of their patients. The subcommittee of the Belgian Hematological Society (BHS) dedicated to the Myeloproliferative Neoplasm decided to review the situation in Belgium.

Method

A questionnaire was sent to the BHS haematologists requesting information about patients who have stopped their treatment with imatinib in conditions comparable to the STIM trial. It concerns patients in chronic phase CML who have stopped their treatment after a minimum of two years of CMR or MMR ($MR^{>3}$) according to determination methods. According to the STIM trial, haematologists have proposed the end of treatment. Patients who have stopped their treatment for toxicity or personal convenience were excluded. Patients were closely monitored for relapse. Patients in confirmed loss of major molecular response were immediately retreated. Eighteen patients were identified, the characteristics of whom are described in *Table 1*. Eight of the eighteen patients (44%) remained in MMR ($MR^{>3}$) from 26 till 58 months after stopping imatinib and ten have lost this MMR; nine within four months after discontinuation, one after 37 months. These patients restarted imatinib and re-achieved $MR^{>3}$ after three to eighteen months of treatment. There was no CML transformation. For the eight patients remaining in $MR^{>3}$ after treatment discontinuation, 6/8 have a $MR^{>3}$ for more than 40 months before discontinuation, 7/8 are women, 4/6 have a low Sokal score and 3/8 were treated with interferon before imatinib.

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Table 1. Patient characteristics.

Age	sex	Sokal score	Time prior IM	interferon	IM duration	Time to MMR	MMR on IM	MMR duration off IM	Time to recovery MMR
29	F	Low	52	+	122	<40	>82	37	3
69	F	High	28	+	121	<40	>81	>58	
69	M	Low	6	+	114	86	28	1	12
65	F	Int	1	-	95	57	39	2	3
55	F	Low	2	-	33	6	28	3	3
67	M	Low	1	-	40	5	35	3	4
58	M	Low	1	-	34	6	28	2	6
54	F		1	-	92	74	24	4	5
63	F	Int	1	-	76	61	25	2	9
31	M	Low	11	+	84	45	39	1	18
38	F	Low	1	-	56	3	54	>51	
60	M	Low	1	+	70	43	28	>42	
46	F	Int	1	-	70	43	28	>40	
52	F	Low	1	-	76	5	60	>40	
65	F	High	9	+	135	11	119	>34	
61	F	Low	1	-	124	8	118	>37	
63	F		16	+	112	18	30	3	8
70	F		1	-	111	5	106	>26	

Age is at the CML diagnosis; Time prior IM is the duration between the diagnosis of CML and the imatinib therapy start; IM duration is the duration of imatinib therapy before the stop; time to MMR is the time required to obtain molecular response >MR^3 (for the first two patients on the list, the time is not precise because the molecular quantification of the bcr-abl transcript was not available at the beginning of their therapy); duration in months.

Discussion

Thus the results of the STIM trial and others series on this topic are confirmed.[4-6] Female gender, low Sokal score and a longer preliminary major molecular remission are favourable prognostic factors to discontinuation of imatinib therapy. Relapses appear rapidly after stopping therapy, but may appear later: for this reason, a regular follow up of the patient is required. All the relapses in our series are responsive when treatment is resumed.

However, in order to allow the discontinuation of treatment in some patients, it is necessary to refine the correct prognostic factors, such as rapidity of initial molecular response obtained with the second-generation TKIs, length of exposure to the TKIs, concomitant therapy or maintenance by immunomodulators such as interferon, development of biomarkers for recurrence risk, etc. Clinicians must also ensure the absence of adverse evolution in patients after cessation of treatment

Key message for clinical practice

1. **Stopping imatinib therapy is possible after long complete molecular response and long exposure to therapy. These patients must be closely monitored for relapse particularly during the first months off therapy. However, stopping tyrosine kinase inhibitor therapy is not a standard of care outside a study.**

and when a new response occurs. Finally, clinicians should consider the patient's choice for the management of their disease, after having discussed both the benefits of the treatment discontinuation and the relapse risk.[7,8]

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