

Long-term molecular responses to imatinib in patients with chronic myeloid leukemia: comparison between complete cytogenetic responders treated in early and in late chronic phase

CML patients who obtain a complete cytogenetic response (CCgR) may harbor different degrees of molecular disease, which are associated with different progression-free survival. We have compared the pattern and the magnitude of the molecular response (MoIR) of 54 early chronic phase (ECP) and of 115 late CP patients who achieved a stable CCgR with IM 400 mg/daily. ECP patients obtained earlier, higher and more sustained MMoIR.

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The striking effectiveness of imatinib (IM, Glivec; Novartis Pharmaceuticals) in chronic myeloid leukemia (CML) has made it the current standard of therapy, with 45% to 60% of patients treated with IM in late chronic phase¹ and 70% to 90% of patients treated in early chronic phase (ECP)² achieving a complete cytogenetic response (CCgR). Monitoring the molecular response (MoIR) by quantitative reverse-transcriptase polymerase chain reaction (RQ-PCR) is of the utmost importance. The prognostic significance of the MoIR has already been established in CML after allogeneic transplantation³ and IFN- α therapy⁴ and has also been confirmed for IM therapy by several reports, which show that the achievement of an early major MoIR (MMoIR), within 12 months from start of IM therapy, is associated with a better progression-free survival^{2,5} and with a more durable CCgR.⁶

We compared the pattern and magnitude of the MoIR of 115 LCP and of 54 ECP patients who achieved a stable CCgR during treatment with IM 400 mg/daily. The patients were enrolled in two different phase II prospective studies, (CML/002/STI571 and CML/011/STI571), of the Italian Co-operative Study Group (ICSG), between July 2000 and June 2001. Median observation time for patients who achieved a stable CCgR is 60 months (range 30-77) for both groups. Cytogenetic studies were performed by standard banding techniques prior to treatment and at 6-12 months intervals thereafter. MoIR was assessed on blood samples every 3-6 months by a standardized RQ-PCR method on an ABI PRISM 7700 Sequence Detector⁹ (Perkin Elmer, Foster City, CA, USA) and ABL was used as housekeeping gene.¹⁰ Samples with Abl Ct values >30 were discarded

Table 2. Distribution by best molecular response of the patients who achieved and maintained a complete cytogenetic response.

Molecular Response	Early chronic phase		Late chronic phase	
	N.	(%)	N.	(%)
Never Major	1	(2%)	24	(21%)
Major, sometimes less than Major	2	(4%)	19	(17%)
Major stable	24	(44%)	44	(38%)
Major, sometimes Complete	25	(48%)	27	(23%)
Complete stable	2	(2%)	1	(1%)
Total	54		115	

6% of early and 38% of late chronic phase patients never achieved a stable major molecular response ($p=0.0003$, Fisher test). RQ-PCR negativity was stable during follow-up in only 2 and 1 cases, respectively.

to ensure RNA was not degraded. MMoIR was defined as a BCR-ABL:ABL ratio <0.05%, corresponding to 0.1% on the International Scale, whereas undetectable BCR-ABL transcript levels were defined as a ratio BCR-ABL:ABL ratio <0.001%, corresponding to this method's lowest level of detectability.

A total of 277 LCP patients were treated with IM after failure of IFN- α : 153/277 (55%) patients achieved a CCgR and 120/153 (77%) are in continuous CCgR after 5 years. Seventy-six ECP patients were treated with IM 400 mg/daily and a variable pegylated IFN- α dose which was discontinued by all patients after a median time of 10 months (range 1-49). Sixty-six ECP patients (87%) obtained a CCgR which was stable in 62 cases (94%). As expected, CCgR rates were significantly higher in the ECP group, being 70% and 82% at 12 and 60 months (vs. 38% and 43% for the LCP group). One hundred and fifteen out of 120 (96%) LCP and 54/62 (87%) ECP patients with stable CCgR were evaluable for MoIR at 60 months. The distribution of the MoIR during the whole study period is reported in Table 1. In ECP patients, the frequency of MMoIR increased up to 74% at 12 months and remained substantially stable at subsequent evaluations. The rate of undetectable Bcr-Abl transcript levels increased from 15% to 26% for a total rate of MMoIR and undetectable Bcr-Abl levels of 98% at 60 months. In LCP patients, the MMoIR rate increased up to 70% at 36 months, while the frequency of undetectable RT-PCR remained low throughout, ranging from 7% to 16%, for a total rate of MMoIR and undetectable Bcr-Abl of 75% at 60 months. Durability of the MoIR is shown in Table 2. Fifty-one out of 54 (94%) ECP patients and 90/115 LCP patients (78%) obtained at least one MMoIR. This was stable in 49 (92%) ECP patients and 71 (61%) LCP patients. Interestingly, the MoIR was never major or was

Table 1. Distribution of molecular response during the whole study period in early (ECP) and late (LCP) chronic phase patients who achieved and maintained a complete cytogenetic response.

Molecular Response	6 months		12 months		24 months		36 months		60 months	
	Percentage of patients		Percentage of patients		Percentage of patients		Percentage of patients		Percentage of patients	
	ECP	LCP								
Less than Major	22	52	6	44	4	31	2	21	2	25
Major	63	38	74	46	78	53	82	70	72	68
Complete	15	10	20	10	18	16	16	9	26	7

Molecular data are available for 54/62 ECP patients and for 115/120 LCP patients. Complete molecular response was defined as undetectable BCR-ABL transcript levels (< 0.001%) by RQ-PCR confirmed by nested PCR. All patients received repeated molecular testing (median 5, range 3-7).

unstable in only 6% of ECP patients (vs. 38% in LCP patients ($p=0.0003$, Fisher's test). Our data confirm that IM therapy led to a high overall rate of CCgR and MMolR in both early and late CP patients, although only a very few patients achieved stable undetectable levels of Bcr-Abl transcript (Table 2). A 5-year follow-up has shown that, despite a comparable cytogenetic response, ECP patients obtained earlier and higher MMolR rates, and that MMolR was more durable, being sustained in 92% of cases vs. 61% in LCP patients. A longer follow-up of all the cases in CCgR with a suboptimal or unstable MolR will clarify if the risk of long-onset resistance is differently distributed among these categories. It is reasonable to suppose that strategies to optimize treatment could be based on IM dose escalation or adoption of alternative tyrosine kinase inhibitors.

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