ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Imatinib: High Dose Versus Standard Dose

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H&O What do we know of the efficacy of imatinib?

EJ Since 2001, imatinib (Gleevec, Novartis) has been the standard of care for patients with chronic myeloid leukemia (CML). In the original phase I trial investigating imatinib therapy, there was no maximum tolerated dose that was reached. Therefore, researchers chose 400 mg because it was a convenient, safe, and active dose.

Cumulative complete response achieved in CML patients after 7 years of imatinib therapy is 87%. At 7 years, the overall survival rate is 86% and 94% if only CML-related deaths are considered.

One of the key studies for imatinib is the International Randomized Study of Interferon Versus STI571 (IRIS) study, which was a phase III, randomized, open-label trial that compared the standard of care at that time, which was interferon and low-dose cytarabine, with imatinib 400 mg daily in patients who had early chronic phase CML. The study was clearly in favor of imatinib in response rates. The study did not show a survival advantage for imatinib because 90% of patients who were on the interferon and cytarabine arm crossed over to imatinib therapy after a median of 9 months.[1]

Another key study was conducted by researchers at the M.D. Anderson Cancer Center, showing that imatinib improved survival compared to standard of care.[2] In this study, adults with newly diagnosed chronic-phase CML were treated with imatinib 400 mg, 600 mg, or 800 mg (400 mg orally twice daily) as frontline therapy. Their outcome was compared with 650 patients treated on interferon-alpha regimens. The complete cytogenetic response rate was 87% for patients who received imatinib and 28% for those who received interferon-alpha regimens. Even when considering the 141 patients who changed from interferon-alpha therapy to imatinib therapy, survival was still significantly better with imatinib (estimated 5-year survival, 88% vs 63%; P=.001). In those treated with imatinib, there was no difference in survival by imatinib daily dose (P=.72). Today, we project the median survival of patients with imatinib therapy to be 25 years.

H&O What are the rationales for dose escalation?

EJ The first rationale for higher imatinib doses can be explained by a clear dose-response relationship, which was shown in a previous phase I study where patients responded more when given higher imatinib doses.[3] Secondly, some mutations of BCR-ABL can be overcome by high-dose imatinib. Specific mutations can still be mildly sensitive to imatinib, and in these cases, a dose increase may be effective. Thirdly, studies have shown that the dose of 600 mg imatinib given to CML patients in the accelerated phase was independently associated with significantly better time to transformation and better survival, compared to patients who received imatinib 400 mg.[4]

Table 1. Response After Dose Increase in Patients With Imatinib Failure

Outcome	Total n=84	Cytogenetic Failure n=63	Hematologic Failure n=21	*P*
Cytogenetic response, n (%)				
Any	50 (60)	47 (75)	3 (14)	<.001
Partial*	10 (14)	8 (16)	2 (10)	.77
Complete	34 (40)	33 (52)	1 (5)	<.001
Rate at 2 years (%)				
EFS	57	65	36	<.001
FFS	29	38	5	<.001
TFS	73	80	51	.004
OS	84	90	67	<.001

EFS=event-free survival; FFS=failure-free survival; OS=overall survival; TFS=transformation-free survival.

*Only patients (n=71) without major cytogenetic response at the time of imatinib dose escalation were evaluable.

H&O In what settings should imatinib dose escalation be considered?

EJ There are 2 settings in which imatinib dose escalation should be considered: the relapse/failure setting and the frontline setting.

Relapse/Failure Setting

In the beginning when imatinib became commercial, it was labeled: if a patient fails imatinib, you can escalate the dose. Based on this fact, our study investigated dose escalation in the setting of failure.[5] We assessed the long-term efficacy of imatinib dose escalation in 84 patients with chronic phase CML. If patients either responded to imatinib 300 mg or 400 mg but later lost their response, or if they did not respond from the start, they were given a higher dose of imatinib (600 mg or 800 mg). And by doing so, we achieved a complete response rate of 40%. Of great importance was that we divided the patients into 2 subgroups: those who had cytogenetic failure and those who had hematologic failure. We found that 52% of patients with cytogenetic failure and 5% of those with hematologic failure achieved complete response (Table 1). Moreover, in patients who had hematologic failure and responded to high-dose imatinib, the responses were transient. Therefore, we concluded that dose escalation can be a good option in patients who already responded to imatinib 400 mg and who had a cytogenetic relapse.

Another study that shows the benefits of high dose imatinib dose escalation is the analysis of the IRIS trial.[6] This study also showed that in a subset of patients (ie, those who had a cytogenetic failure) dose escalation can induce sustained responses. Response and survival were analyzed in a cohort of newly diagnosed, chronic phase CML patients who were enrolled in the IRIS trial, began treatment with imatinib at a dose of 400 mg daily, and subsequently underwent dose escalation to either 600 mg or 800 mg daily. Among all 106 patients who underwent dose escalation, the rates of freedom from progression to accelerated phase/blast phase and overall survival were 89% and 84%, respectively, at 3 years after dose increase. This was a retrospective analysis, but the results were in concordance with previous findings and supported imatinib dose escalation as an appropriate option for patients with chronic phase CML who were experiencing suboptimal cytogenetic response or resistance.

Frontline Setting

Imatinib has also been assessed in the frontline setting. The key study investigating standard dose imatinib versus high dose imatinib is the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) trial, a prospective, open-label, randomized (2:1 ratio) phase III trial that studied the efficacy of imatinib 400 mg versus 800 mg in chronic phase CML patients.[7] The primary endpoint was the rate of major molecular response at 12 months; and secondary endpoints included rates of complete hematologic response, complete cytogenetic response, time to complete cytogenetic response and major molecular response, progression to accelerated phase/blast crisis, event-free survival, overall survival, imatinib dose-intensity, pharmacokinetics, and safety.

In the intent-to-treat population, a significantly higher rate of complete cytogenetic response and major molecular response in the high-dose arm was recorded at 6 months. However, at 12 months, although the

response rates were still higher than those of the standard dose arm, the differences were not significant; the study could not prove a significant major molecular response improvement at 12 months. It is still too early to conclude on the secondary endpoints (eg, survival rates), and we are waiting for the data to mature.

H&O How does imatinib dose escalation compare with other options such as second generation tyrosine kinase inhibitors (TKIs)?

EJ Other than dose escalation, we have other options available today: second generation TKIs—nilotinib (Tasigna, Novartis) and dasatinib (Sprycel, Bristol-Myers Squibb). These agents are currently being assessed in the frontline setting. In patients with imatinib failure, studies have shown that dasatinib induced major cytogenetic response and complete cytogenetic response rates of 55% and 45%, respectively, at 24 months. Nilotinib induced major cytogenetic response and complete cytogenetic response rates of 55% and 41%, respectively, at 18 months. The 2-year survival in our study was 84% for those who received dose escalation, whereas the 2-year survival with dasatinib was reported to be 92%, and 91% (at 18 months) with nilotinib.[8,9] However, direct back-to-back analyses have not been performed among these options, and it is important to consider inaccuracies that may be caused by comparisons between independent studies performed at different times and places. Also, it is important to note that most patients reported in studies investigating second-generation TKIs had already failed imatinib dose escalation.

H&O How do you determine whether a patient should be dose escalated or switched to a second generation TKI?

EJ I believe that the decision depends on the patient's previous response to imatinib. If someone had a hematologic failure, I am not going to dose escalate. If someone initially responded to imatinib, then failed, I may escalate. Other criteria to consider are tolerance/side effects and mutation profiles, meaning those who have no mutation and had previously responded to imatinib 400 mg may benefit from dose escalation. If someone had a mutation—resistance—to imatinib, dose escalation may not be the best option, and therefore I would switch to nilotinib or dasatinib.

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