5 Minute JournalClub

Key ASCO Presentations
Issue 6, 2010

Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myelogenous Leukemia (CML-CP)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Recognize dasatinib as a potential option in the front-line treatment of CML-CP.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Hagop M Kantarjian, MD
Chairman and Professor, Leukemia Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Paid Research: Bristol-Myers Squibb Company, Genzyme Corporation, Novartis Pharmaceuticals Corporation.

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This program is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology and Millennium Pharmaceuticals Inc.

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To go directly to the slides and commentary, **click here**.

When we launched our *Hematologic Oncology Update* audio series several years ago, one of the first investigators I interviewed was Dr Hagop Kantarjian, and from the moment he began to answer what must have seemed like sophomoric questions, I was transfixed and almost held my breath in anticipation of his every response.

During my most recent chat with this MD Anderson legend, we focused on three groundbreaking ASCO presentations on CML, all of which he coauthored. Two of these studies have been subsequently published in *The New England Journal* (Dr K was first author on one), along with a thought-provoking editorial by Charles Sawyers.

For almost a decade, imatinib has been the pillar of CML treatment, and while the agent produces an approximately 65 percent one-year complete cytogenetic response rate and a major improvement in overall survival, there is room for improvement. This possibility became potentially achievable when significant activity was observed with the more potent second-generation TKIs, nilotinib and dasatinib, in patients with disease progression on imatinib.

In response to these important data, several front-line trials were initiated with these agents. For each of these trials, a key endpoint was major molecular response — defined as a three-log reduction of BCR-ABL from baseline (99.9 percent). The first to report was a study of **nilotinib versus imatinib** unveiled in December at ASH and then updated at ASCO, where **a similar trial comparing dasatinib to imatinib** was also presented. The bottom line is that both of these agents produced superior 12-month complete cytogenetic and major molecular responses along with clinically significant reductions in transformation to accelerated phase or blastic crisis. Dr Kantarjian noted that these impressive findings involve early surrogate endpoints and it will be critical to look at three- to five-year event-free survival. Following closely is yet another TKI, **bosutinib**, which as we heard at ASCO proved to have significant activity in patients with disease progression on TKIs. The Phase III up-front comparison to imatinib is due to report very soon.

Dr Kantarjian agrees with Dr Sawyers' editorial that a key issue moving forward will be the one to two percent a year of patients on TKIs who develop new mutations in the BCR-ABL binding site — particularly T315I lesions, which result in resistance to TKIs.

For these important patients, the key may be to add new agents to the TKIs, and a number are in development.

Next up on 5-Minute Journal Club: Another fascinating example of oncogene addiction and TKIs: EML4-ALK and crizotinib in non-small cell lung cancer... and more.

Neil Love, MD
Research To Practice
Miami, Florida

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Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

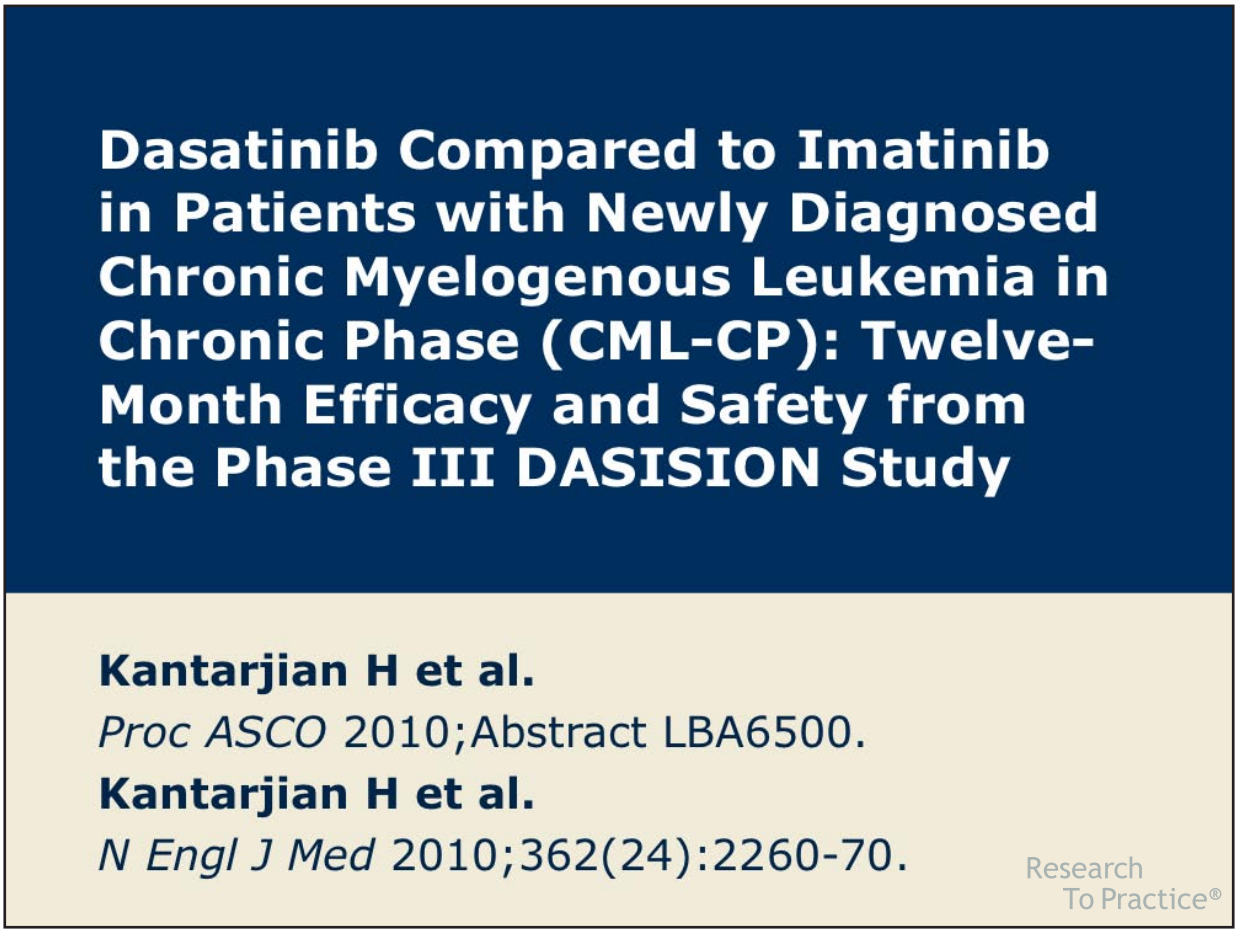
Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myelogenous Leukemia (CML-CP)

Presentations discussed in this issue

Kantarjian H et al. **Dasatinib compared to imatinib in patients with newly diagnosed chronic myelogenous leukemia in chronic-phase (CML-CP): Twelve-month efficacy and safety from the phase III dASISION study.** *Proc ASCO* 2010;**Abstract LBA6500**.

Kantarjian H et al. **Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.** *N Engl J Med* 2010;362(24):2260-70. **Abstract**

Slides from a presentation at ASCO 2010 and transcribed comments from a recent interview with Hagop M Kantarjian, MD (6/30/10)

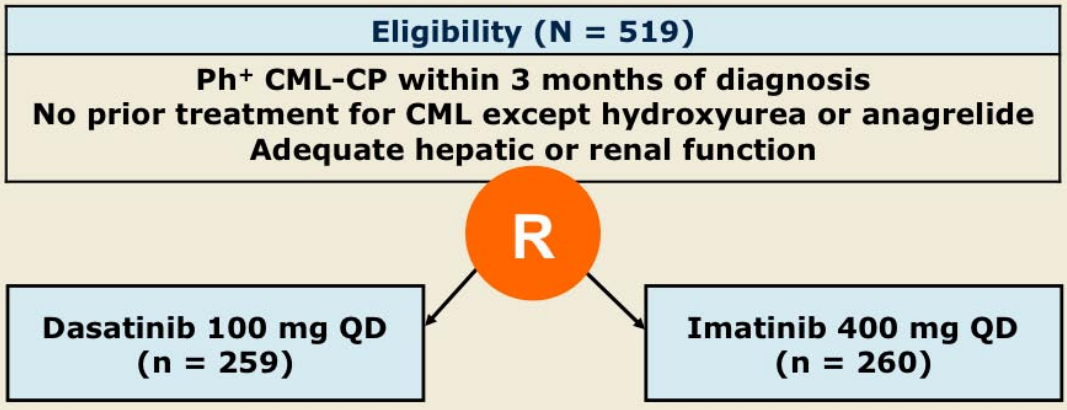


Background

- Achieving complete cytogenetic response (CCyR) and/or major molecular response (MMR) by 12 months on imatinib is associated with superior long-term progression-free survival (PFS) (*NEJM* 2006;355:2408, *JCO* 2008;26:3358).
- Dasatinib induced high rates of CCyR and PFS in patients with CML after IM failure (*Haematologica* 2010;95:232).
- Phase II single-arm study demonstrated high rates of CCyR and MMR with dasatinib used in the first line for CML-CP (*JCO* 2010;28:398).
- **Current study objective:**
  - Assess the efficacy and safety of dasatinib as first-line treatment for patients with CML-CP.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

DASISION: Phase III Trial Schema



Primary endpoint was confirmed CCyR (defined as confirmed CCyR on two consecutive assessments at least 28 days apart) by 12 months.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

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Response Rates

	Dasatinib (n = 259)	Imatinib (n = 260)	*p*-value
Confirmed CCyR by 12 months[1]	77%	66%	0.007
CCyR by 12 months[2]	83%	72%	0.001
MMR by 12 months	46%	28%	<0.0001
MMR at any time	52%	34%	<0.0001
Progression to accelerated/ blastic phase	1.9%	3.5%	—

[1] Confirmed CCyR is defined as CCyR detected in two consecutive assessments. The second confirmation could have occurred after 12 months.
[2] CCyR defined as CCyR detected at least once in at least 20 metaphases.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

Selected Drug-Related Adverse Events

	Dasatinib (n = 258)		Imatinib (n = 258)	
Adverse Event	All Grades	Grade 3/4	All Grades	Grade 3/4
Neutropenia	65%	21%	58%	20%
Anemia	90%	10%	84%	7%
Thrombocytopenia	70%	19%	62%	10%
Superficial Edema	9%	0%	36%	<1%
Pleural Effusion	10%	0%	0%	0%
Muscle Inflammation	4%	0%	17%	<1%
Vomiting	5%	0%	10%	0%

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

Conclusions

- Dasatinib has superior efficacy compared to imatinib in first-line CML-CP.
  - Superior confirmed CCyR, CCyR and MMR
  - Lower rate of progression to accelerated/blastic phase
  - Faster rates of confirmed CCyR and MMR
    - Hazard ratio for shorter time to confirmed CCyR: 1.5, $p < 0.0001$
    - Hazard ratio for shorter time to MMR: 2.0, $p < 0.0001$
- Dasatinib was well tolerated.
- Longer follow-up may demonstrate better long-term outcomes with dasatinib in patients with CML-CP based on the association of achieving CCyR by 12 months and improved PFS in response to imatinib.

Kantarjian H et al. *Proc ASCO* 2010;Abstract LBA6500; Kantarjian H et al. *N Engl J Med* 2010;362(24):2260-70.

Investigator comment on the results of DASISION: A Phase III study of dasatinib versus imatinib in newly diagnosed CML-CP

This was a two-arm randomized trial of orally administered dasatinib at the dose of 100 mg per day, which was found in the follow-up studies to be as effective and probably less toxic than 70 mg twice a day, the dose at which dasatinib was originally approved. The second arm was the standard approach of imatinib 400 mg per day.

The primary endpoint of the study was the incidence of complete cytogenetic response by 12 months, and the study met its endpoints. There was a significantly superior rate of complete cytogenetic response by 12 months with dasatinib compared to imatinib, a significantly higher incidence of major molecular response and a trend for a reduction in the rate of progression to accelerated phase and blastic phase.

Additionally, we observed less of the bothersome toxicities with dasatinib. There were lower incidences of muscle aches, nausea, vomiting and skin rash. We did observe a little more Grade 3/4 thrombocytopenia, and 10 percent of the patients had pleural effusions, which were all mild to moderate and reversible with modifications of the dose and interruptions.

Interview with Hagop M Kantarjian, MD, June 30, 2010