Pharmaceutical Management of Chronic Myeloid Leukemia:

Finding the Optimal Strategy

Needs Assessment

The introduction of tyrosine kinase inhibitors (TKIs; imatinib, dasatinib, nilotinib) has transformed clinical management of chronic myeloid leukemia (CML). Since the approval of imatinib in 2001 for frontline treatment of Philadelphia chromosome-positive, chronic phase CML (CML-CP), investigators have been refining our understanding of the utilization of TKIs to obtain optimal outcomes. Although most CML patients receiving TKI therapy achieve clinically significant hematologic, cytogenetic, and molecular responses, the durability of response is limited by the development of mutation-induced drug resistance and drug-related toxicities. ***Providers are challenged to stay abreast of the evidence-based findings that inform treatment choices for optimal outcomes.***

Gap Analysis

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
A significant portion of physicians do not follow CML treatment guidelines (lack of **performance**), perhaps due to lack of **knowledge** or **competence**	*Recent survey; Expert opinion*	Review recent practice guidelines (NCCN 2009, ENL 2008, ESMO 2009)	3/4/5 (Knowledge/ Competence/ Performance)
Providers lack the **knowledge** of findings from recent clinical trials that would inform their **competence** and **performance** in applying treatment guidelines	*Literature review; Expert opinion*	Revisit current definitions for inadequate response to therapy with imatinib	3/4/5 (Knowledge/ Competence/ Performance)

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
Providers lack **knowledge** of 7-year outcomes from the IRIS study, or the **competence** that demonstrates their understanding of the clinical implications of the findings	*Literature review; Expert opinion*	Review 7-year analysis of IRIS outcomes	3/4 (Knowledge/ Competence)
Providers lack **knowledge** of markers for long-term outcomes that can inform optimal treatment strategies early in the course of therapy	*Literature review; Expert opinion*	Review MD Anderson Cancer Center study findings (*Blood,* June 2009)	3/4/5 (Knowledge/ Competence/ Performance)
Providers lack **knowledge** of efficacy and safety outcomes with second generation TKIs as frontline therapy for CML-CP	*Literature review; Expert opinion*	Review outcomes from clinical studies of second generation TKIs in newly diagnosed, previously untreated patients with CML-CP	3/4/5 (Knowledge/ Competence/ Performance)
Providers lack **knowledge** of the selective role TKI drug resistant mutations play in suboptimal outcomes and the **competence** to make informed adjustments to prevent disease progression	*Literature review; Expert opinion*	Review outcomes from clinical studies of specific TKI regimens that identify secondary resistance associated with BCR-ABL mutations	3/4/5 (Knowledge/ Competence/ Performance)

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
Providers lack **knowledge** of potential future treatments for CML and how they may augment the current anti-CML armamentarium.	*Literature review; Expert opinion*	Review promising agents in Phase 2/3 stage of development	3 (Knowledge)

CML is a myeloproliferative neoplasm arising at the pluripotent stem cell level. It is characterized by the Philadelphia chromosome, a product of chromosomal translocation that rearranges genetic sequences from chromosomes 9 and 22, positioning the Break-point Cluster Region (BCR) next to the Abelson (ABL) gene. (Jabbour 2009 *Targ Oncol*) This translocation fuses the 2 genes, coding for the constitutively active protein, BCR-ABL tyrosine kinase. (Jabbour 2009 *Targ Oncol*)

BCR-ABL is itself genetically unstable, resulting in mutations commonly seen in a variety of other cancers. (Jabbour 2009 *Targ Oncol*) The carcinogenic nature of BCR-ABL tyrosine kinase and protein products of these genetic mutations is believed to be linked to their disruption of signaling pathways and deregulation of cellular homeostasis. (Jabbour 2009 *Targ Oncol*)

Inhibition of BCR-ABL tyrosine kinase is the clinical rationale behind the development of imatinib for the treatment of CML. Based on superior responses and survival with imatinib over interferon-alpha in the landmark IRIS study, treatment of CML has been radically changed and this first TKI has become the new standard of care for CML in chronic phase (CML-CP). (O'Brien 2003 *NEJM*)

Evidence-based guidelines have been evolving since the introduction of imatinib, refining practice management for optimal outcomes in the TKI era. Recommendations for frequent cytogenetic analysis and molecular monitoring ensure the detection of suboptimal responders. (*NCCN, ELN*, Baccarani 2009 *Ann Oncol*) Early recognition of patients not achieving a

complete cytogenetic response (CCyR) or major molecular response (MMR) is critical for making regimen adjustments shown to improve outcomes. (Quintás-Cardama 2009 *Blood*) Unfortunately, findings from a recent survey suggest a significant portion of CML treaters do not follow these management guidelines. (Jabbour 2009 *Mayo Clin Proc*; Jabbour 2009 *Targ Oncol*) ***Healthcare providers need to increase their performance in following evidence-based guidelines for optimal outcomes in CML.***

In keeping with the evolution of evidence-based guidelines, healthcare providers should stay abreast of recent clinical trial outcomes and their implications for defining suboptimal response to and failure of imatinib therapy. Response rates are currently reported as best achievements among only the patients remaining on treatment, which distorts both the percent of cumulative incidence and durability of outcomes. (Quintás-Cardama 2009 *Nature Rev Clin Oncol*; Palandri 2009 *Clin Cancer Res*) There continues to be a debate about how to characterize clinical responses that are valid markers for event free progression and overall survival. (Kantarjian 2008 *Cancer*) ***Healthcare providers need to increase their competence in analyzing current evidence-based guidelines in light of newly reported study outcomes.***

Among patients remaining on the IRIS imatinib protocol at year 7, the estimated event-free survival was 81%, freedom from progression to accelerated phase (AP) or blast crisis (BC) was 93%, and overall survival was 86%. (O'Brien 2008 *ASH abs*) However, approximately 35% of patients randomized to the imatinib treatment arm in IRIS failed to reach or sustain CCyR. (O'Brien 2008 *ASH abs*) Furthermore, a large portion of patients, including those who did achieve CCyR, had residual molecular disease noted by the presence of leukemic stem cells. (Quintás-Cardama 2009 *Nature Rev Clin Oncol*) ***Healthcare providers are in need of the knowledge of the long-term outcomes and safety reported in the 7-year analysis of IRIS.***

Markers of long-term outcomes are necessary for assessment early in the course of therapy. The 5-year report of the IRIS study concluded that achievement of CCyR at 12 months and reduction of BCR-ABL transcripts of less than 3 logs at 18 months was predictive of a lack of disease progression at 60 months. (Druker 2006 *NEJM*) However, a recently reported study suggests patients who do not achieve MMR (reduction of BCR-ABL1/ABL1

transcripts ratio <1%) after 3 months of imatinib (400 mg/d or 800 mg/d) are at significant risk of disease progression and alternate treatment should be considered for these patients. (Quintás-Cardama 2009 *Blood*) ***Healthcare providers are in need of the knowledge of markers for long-term outcomes that can inform optimal treatment strategies early in the course of therapy.***

An option to improve suboptimal responses to imatinib is to increase the dose. Compared with standard-dose imatinib (400 mg/d), high-dose imatinib (800 mg/d) resulted in significantly faster onset and greater incidence of MMR in the TOPS study (Cortes 2008 ASH 335), even in patients who failed standard-dose imatinib, (Jabbour 2009 *Blood*) or had intermediate- (Castagnetti 2009 *Blood*) or high-risk Sokal scores in the GIMEMA study. (Baccarani 2008 ASH 185) When analyzed by trough plasma imatinib levels, the threshold for response was identified as ≥1000 ng/mL and the trough level associated with significantly faster onset and greater incidence of MMR was 1,165 ng/mL. (Guilhot 2008 ASH 447) ***Healthcare providers are in need of the knowledge of outcomes with high-dose imatinib.***

Because a substantial portion of patients treated with imatinib at any dose will need alternative therapy, there is a need for frontline treatment options for CML patients with outcomes equivalent to imatinib and greater durability of response. Second generation TKIs are currently approved for second-line treatment of chronic phase and accelerated phase CML (dasatinib and nilotinib), and CML in blast crisis (dasatinib only). (Dasatinib PI 2009, Nilotinib PI 2007) Phase II studies of dasatinib (Cortes 2008 ASH abs 182), and nilotinib (Cortes 2008 ASH abs 446; Rosti 2008 ASH abs 181) are studying the rate and incidence of CCyR and MMR in CML-CP. After 3, 6 and 12 months of treatment, dasatinib 100 mg/d resulted in significantly faster and greater incidence of CCyR than imatinib 400 mg or 800 mg. (Cortes 2008 ASH abs 182) Nilotinib 400 mg BID produced CCyR in nearly all patients as early as 3 months, significantly greater CCyR than imatinib 400 mg or 800 mg at 3, 6, 12, 18, and 24 months of treatment. (Cortes 2008 ASH abs 446), and 74% achieved MMR after 6 months. (Rosti 2008 ASH abs 181) However, toxicities with nilotinib forced dose reductions (32%), treatment interruptions (36%), and treatment discontinuations (6%). (Rosti 2008 ASH abs 181) ***Healthcare providers are in need of the knowledge of efficacy and safety outcomes with second generation TKIs as frontline therapy.***

A relapse of molecular disease during TKI therapy can indicate TKI secondary resistance, which is primarily caused by point mutations in the BCR-ABL gene. (Jabbour 2009 *Targ Oncol*) At present, more than 50 mutation sites and 70 point mutations associated with drug resistance have been found in CML patients. (Redaelli 2009 *J Clin Oncol*) In vitro studies have shown that both dasatinib and nilotinib can inhibit all BCR-ABL mutations except the T315I point mutation, which is resistant to all TKIs. (Jabbour 2009 *Mayo Clin Proc*) However, clinical studies have revealed selective differences in mutation susceptibility to second-generation TKIs. For example, dasatinib treatment failures have been associated with V299L, F317L and T315I mutations and nilotinib failures with Y253F, E255V, E255K, F359V and T315I mutations. (Jabbour 2009 *Mayo Clin Proc*; Redaelli 2009 *J Clin Oncol*) These findings suggest optimal treatment regimens could be individualized, based on frequent screenings for drug resistant mutations. ***Healthcare providers are in need of the knowledge of the role drug resistant mutations play in suboptimal outcomes and the competence to make informed adjustments to prevent disease progression.***

There are a number of anti-CML agents in the pipeline that may be introduced in the near future. A fourth TKI, bosutinib, is in Phase 3 stage of development. Like dasatinib, bosutinib is a dual inhibitor of BCR-ABL and Svc family kinases (SFK), but is also not effective against the T315I mutation. (Jabbour 2009 *Targ Oncol*) Several third generation TKIs / multikinase inhibitors are under development to target the difficult-to-treat T315I mutation. MK-0457 and PHA-739358, which are dual BCR-ABL / Aurora kinase inhibitors, are currently in Phase 2 trials. (Quintás-Cardama 2009 *Nature Rev Clin Oncol*) Anti-CML agents that may be useful as monotherapy or in combination regimens with TKIs are non-TKIs, such as omacetaxine (homoharringtonine), decitabine, tipifarnib, and lonafarnib. (Jabbour 2009 *Mayo Clin Proc*) Omacetaxine has demonstrated efficacy against T315I and BCR-ABL-positive leukemic stem cells. (Jabbour 2009 *Targ Oncol*; Quintás-Cardama 2009 *Nature Rev Clin Oncol*) ***Healthcare providers are in need of the knowledge of potential future treatments for CML and how they may augment the current anti-CML armamentarium.***

IRIS: International Randomized Study of Interferon Versus STI751.
TOPS: Tyrosine Kinase Inhibitor Optimization and Selectivity.

GIMEMA: Gruppo Italiano Malattie Ematologiche Ddell'Adulto (Italian Group for Hematologic Malignancies of the Adult).

Learning Objectives

- Familiarity with the most recent guidelines for the clinical management of CML
- Knowledge of the clinical parameters that define the various inadequate responses to imatinib, and the treatment implications of each
- Knowledge of the limitations of therapy with imatinib seen at the IRIS 7-year follow-up
- Understanding of the treatment options after an inadequate response to imatinib
- Awareness of the newer anti-CML agents in clinical development and the clinical advantages they may confer

Intended Audience

- Hematology oncologists
- Oncology pharmacists (advanced practice)
- Managed care pharmacists

Proposed Agenda

I. Introduction by Program Chair

II. CML Practice Guidelines

- National Comprehensive Cancer Network (2009)
- European LeukemiaNet (2008)
- European Society for Medical Oncology (2009)

III. Revisit clinical definitions for inadequate response to therapy with imatinib

- Primary resistance
- Secondary resistance
- Suboptimal response
- Intolerance

IV. Recent clinical trial outcomes with TKI regimens

- Management of imatinib therapy to overcome inadequate response
  - 7-year update of IRIS study

        - Early predictors of long-term response: timing of complete cytogenetic response (CCyR) + major molecular response (MMR)
        - CML-CP treated with high-dose (800 mg) vs standard dose (400 mg)
    - Second generation TKIs
        - Frontline option for CML-CP?
        - Treatment choices guided by BCR-ABL1 kinase domain mutations

V. Pipeline therapies

- Second generation TKI: bosutinib
- Third generation TKIs: multikinase inhibitors
- Non-TKI anti-CML agents: omacetaxine (only pharmacologic option shown to overcome T315I mutation)

VI. Questions and answers

VII. Concluding remarks by Program Chair

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All faculty members will be screened for possible conflicts of interest (COI) and the program will be executed in a manner that is consistent with OIG, FDA, ACCME, and ACPE standards and guidelines.

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