Chronic Myelogenous Leukemia (CML) Drugs
Oral Medications

Executive Summary

- Agents used in CML have a similar mechanism of action and have led to improvements in overall survival. While agents approved since imatinib (Gleevec) can have deeper and improved cytogenetic and molecular responses in the first-line setting, this has not translated to clinically significant improvements in overall survival when compared to imatinib.
- Soon after approval, imatinib became the standard of care for CML. As a result, second generation agents seeking approval used imatinib as the comparator in their pivotal trials. Patients can have disease progression on imatinib due to resistance or mutation, which then requires advancing to other CML agents. Though well tolerated overall, patients do switch agents due to toxicity.
- Imatinib is the most frequently used agent; however, the newer agents, particularly dasatinib (Sprycel) and nilotinib (Tasigna), are also utilized first line with high quality evidence supporting that approach. Nilotinib and dasatinib are preferred by some providers in that setting and recommended as options in practice guidelines.
- Overall, the tyrosine kinase inhibitors (TKIs) have slightly different but favorable side effect profiles. However, some of the newer agents have had significant safety issues that have limited their use. Bosutinib and ponatinib are considered second line agents with specific indications for certain mutations or use only after failure of first line therapies.
- Selecting the appropriate TKI depends on many factors, including patient characteristics, provider experience, disease phase, primary or secondary resistance to TKI, side effect profile, and relative effectiveness against mutations.
- In the first line setting, one or two agents could provide for the majority of patients in the MHS population. For the entire disease course and progression, all products are required on the formulary to meet the needs of the entire MHS population.

Background

- No CML subclass or individual drug review has been previously completed. As a result, none of the products that are part of this review have been previously designated nonformulary.
- See Table 1 for drugs in the class.
- There are approximately 6,000 CML cases per year in the United States with a median age at diagnosis of 64. The diagnosis is often made when patients are in the chronic phase of the disease and after laboratory measurement of a complete blood count revealing leukocytosis triggers additional testing. Karyotyping, FISH, PCR, and bone marrow biopsy can be used to definitively diagnose. There are three distinct phases of the disease: chronic, accelerated, and blast. Prognosis worsens as the disease progresses.
- Patients with CML have an abnormally large number of white blood cells. In most patients, the defect results from a specific problem in the genetic instructions in these cells. Patients have a chromosomal rearrangement known as the Philadelphia chromosome, where chromosome 9 and 22 exchange fragments. This hallmark of the disease allows for the creation of a BCR-ABL fusion gene which encodes a protein that causes excessive cell division and is the target of TKIs.
- The resultant protein's activity in the cell is blocked by the TKIs. The initial goal of therapy is achievement of a hematologic response followed by a complete cytogenetic response, and eventually a major molecular response. These responses are measured at pre-specified intervals. Failure to achieve guideline recommended goals helps drive agent selection and switching.
- Five-year overall survival prior to the advent of TKIs was 42–57%. Since their development, TKIs have replaced allogeneic stem cell transplant and its attendant 25% mortality and CML overall survival has improved to nearly 90%.
- MHS expenditures and utilization of all oral oncology products, including CML agents, are increasing.
- Imatinib received FDA approval for use in CML in 2001 and has since been able to obtain additional oncologic indications. Imatinib as a result of earlier approval has a dataset with eight years of outcomes. The second set of agents to be approved, dasatinib and nilotinib, promise deeper cytogenetic and molecular responses. While some providers shifted to these newer agents in the first line setting, the overall survival difference between imatinib and two newer first line agents has not been found to be statistically significant. The two newer agents do appear to have a clinical benefit over imatinib in a higher risk subset of patients and guidelines support considering their utilization in this cohort of patients.

Table 1: Drugs in the CML Class

CML Agents					
Generic	**imatinib**	**dasatinib**	**nilotinib**	**bosutinib**	**ponatinib**
Brand	**Gleevec**	**Sprycel**	**Tasigna**	**Bosulif**	**Iclusig**
Manufacturer	Novartis	Bristol Myers Squibb	Novartis	Pfizer	ARIAD
Approval (yr)	2001	2006	2007	2012	2012
Dose (mg)	400	100	300	500	45
Frequency	Daily	Daily	Twice daily	Daily	Daily
Indication	Adult newly diagnosed Ph+ CML Chronic Phase			2nd line	2nd Line or +T315I

- While there are no prior authorizations currently in place for any of the CML agents, all have quantity limits at mail and retail. Ponatinib is restricted to one pharmacy and bosutinib is restricted to specialty pharmacies.
- There are no generic formulations currently approved by the FDA for any of the CML agents. Imatinib is expected to have generic competition in early 2016. Sun Pharmaceuticals and Apotex have tentative FDA approval for generic imatinib.
    - FDA considers overall survival and progression free survival key endpoints in the treatment of CML. The use of surrogate endpoints, cytogenetic response and molecular response, is common in the pivotal trials used to obtain approval and have been linked to overall survival.
- Agents or interventions not reviewed but used in treatment of CML: hydroxyurea/busulfan, omacetaxine (Synribo), interferon alfa ± cytarabine, human stem cell transplant, and total body irradiation.
- Monitoring response is key to therapeutic decision making. There are three routine methods for measuring disease response. Hematologic response is a measure of white blood cell count and platelet counts with a goal to normalize after 2-3 months of treatment. Cytogenetic response is an assessment of bone marrow or FISH analysis to determine the number of Ph+ chromosomes. Molecular response is a measurement of BCR-ABL transcript levels relative to a control gene. As the level decreases, there is less disease burden. Currently peripheral blood PCR is the preferred method for monitoring as it does not require bone marrow biopsy. A three-month post treatment initiation BCR-ABL PCR at less than 10% of baseline has been associated with a good prognosis. A 12-month evaluation showing a complete cytogenetic response is another prognostic indicator.

Summary of the Evidence

Efficacy:

- There are currently three drugs approved in the United States for frontline therapy of CML: imatinib, nilotinib, and dasatinib. Imatinib is associated with improved survival, with results from the International Randomized Study of Interferon versus STI571 trial (IRIS) showing overall survival (OS) of 85% at eight-year follow-up. In IRIS, 1106 newly diagnosed patients were randomized to imatinib or interferon-alpha plus low-dose cytarabine, the prior standard of care. Complete cytogenetic response (CCyR) at 12 months was 73.8% and 8.5%, respectively. The study and long-term follow-up data showed that imatinib induces high durable responses with a low relapse rate in a large portion of patients with Chronic Phase (CP) CML (see Table 2 for comparative statistics).
- Both nilotinib and dasatinib have been compared directly to imatinib but not to each other in large randomized trials in newly diagnosed CML patients. Both second generation TKIs have shown improvement in complete cytogenetic response at one and two years compared with imatinib. After five years follow-up, both second generation TKIs showed an increased percentage of patients achieving major molecular response.
- In the DASISION trial, 76% of dasatinib patients achieved MMR by five years compared with 64% of imatinib patients. Confirmed CCyR at 12 months for dasatinib was 77% versus 66% for imatinib. While there was a trend in favor of dasatinib, progression to accelerated or blast phase was not statistically different between the two groups (2% versus 3.5%). In the ENESTnd trial, 77% of nilotinib patients achieved MMR by five years compared with 60% of imatinib patients. Confirmed CCyR at 12 months for nilotinib was 80% at 300 mg dose versus 65% for imatinib. Additionally, the ENESTnd trial demonstrated a significant reduction in progression for patients who had received nilotinib.
- In the patients with imatinib resistance or intolerance, dasatinib, nilotinib, or bosutinib can be used. Intolerance or resistance to nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib).

Table 2: Key Statistics from Pivotal TKI Trials

Trial	Drug	N	CCyR @1 yr	AP/BP Progression	MMR	eFS	OS
IRIS (Imatinib)	**Imatinib** vs IFN-cARA	553 553	74% 8%	8% (18 mo) 26% (18 mo)	86% (8yr) 15% (18 mo)	81% (8yr)	85% (8yr) 93% nonCML
ENESTnd (Nilotinib)	**Nilotinib 300 bid** **Nilotinib 400 bid** Imitanib 400	282 281 283	80% 78% 65%	3.9% (6 yr) 2.1% (6 yr) 7.4% (6 yr)	77% (5yr) 77% (5yr) 60% (5yr)	95% (5yr) 97% (5yr) 93% (5yr)	94% (5yr) 96% (5yr) 92% (5yr)
DASISION (Dasatinib)	**Dasatinib** 100 Imitanib 400	259 260	77% 66%	2.3% (2 yr)	76% (5yr) 64% (5yr)	90% (4yr) 90% (4yr)	93% (4yr) 92% (4yr)
BELA (Bosutinib)	**Bosutinib** 500 Imatinib 400	250 252	70% 68%	1% (2 yr) 2% (2 yr)	59% (2yr) 49% (2yr)	97% (2yr) 95% (2yr)	92% (2yr) 88% (2yr)
EPIC* (Ponatinib)	**Ponatinib** Imatinib	155 152	100% 86%		41% 18%		
CCyR = Complete Cytogenetic Response; AP/BP = Accelerated phase/blast phase; MMR = Major Molecular Response; eFS= free from progression to accelerated and blast phase; OS = Overall survival; * = planned n= 500, median follow-up 5 mo., study terminated d/t safety October 13							

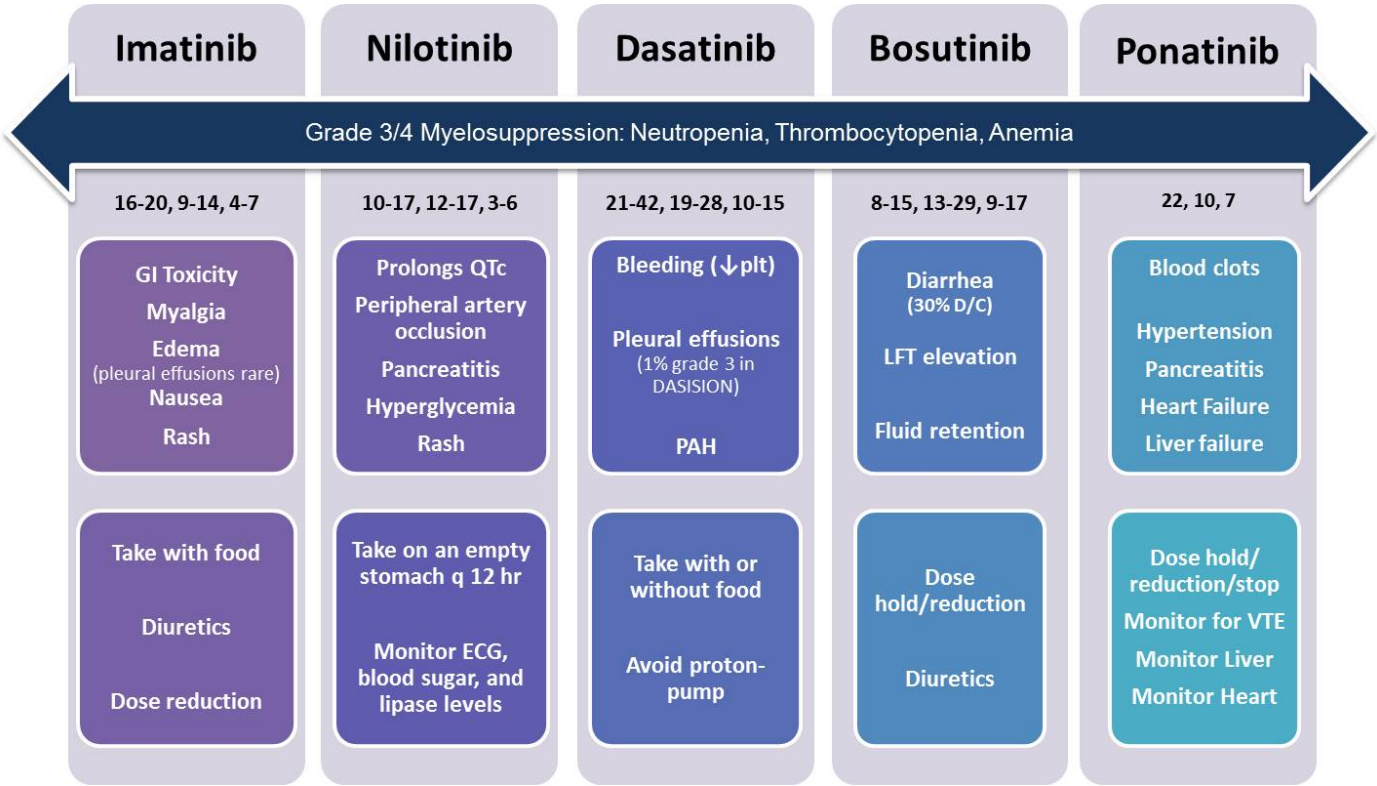
Guidelines:

- NCCN: Imatinib, nilotinib, and dasatinib receive Category 1 recommendations for first line therapy options in newly diagnosed CP-CML. Based on subanalyses of trials, intermediate and high risk patients (as determined by Sokal and Hasford scores) may benefit from dasatinib or nilotinib. Longer-term follow-up is needed to determine whether dasatinib and nilotinib should be implemented as standard first line therapy in such a risk-adapted fashion. In general, choice of therapy may depend on risk score, physician's experience, age, ability to tolerate therapy, and presence of comorbid conditions.
- NICE: A technology appraisal from the National Institute for Health and Care Excellence (NICE) in April 2012 evaluated the clinical and cost effectiveness of the CML agents. The guidance from NICE appraisal was as follows:
  - Imatinib and nilotinib recommended as options for first line treatment of Ph+ CML. Nilotinib recommendation was predicated on availability of manufacturer discount. Dasatinib was not recommended as first line treatment choice.

Safety:

- The CML agents all share a common molecular target, BCR-ABL1, but their relative affinities and binding to other kinase targets influences their individual adverse event profiles. The toxicities of the drugs differ and are considered when selecting amongst these drugs. Major grade 3/4 side effects typically occur during first phase of treatment and are manageable (see Fig. 1 for management options). Anemia, thrombocytopenia, and neutropenia are issues common to all the agents. The grade 3/4 myelosuppression percentage ranges from available studies are included in the figure below. Imatinib and dasatinib are well tolerated overall. Imatinib has been noted to have fluid retention, but it is typically found to be peripheral in nature. Dasatinib has been associated with issues with pleural effusion. Nilotinib has a black box warning for QT interval prolongation, and has been associated with pancreatitis and hyperglycemia issues. Bosutinib has a greater number of gastrointestinal issues than the other TKIs. In October 2013, an FDA Drug Safety Communication revealed an increase in cumulative incidence of thrombotic events with use of ponatinib. As a result, ponatinib is indicated in patients with T315I mutation and for treatment of CML when no other TKI is indicated.
- All the TKIs are extensively metabolized in the liver by cytochrome P450 enzymes. Drugs that induce or inhibit CYP3A4 or 3A5 may alter the therapeutic effect of TKIs. Overall drug interaction profiles are similar.

Figure 1: Myelosuppression Event Frequency, Common Adverse Events, and Management Nuances



Conclusion

- All the TKIs have resulted in unprecedented hematologic, cytogenetic, and molecular response compared to previously available therapies. Imatinib and the second generation agents have shown overall survival benefits with up to eight years of extended trial data. Imatinib and the second generation agents are widely used and preferred in first line use in CP CML. The second generation agents have shown a deeper, faster response, but that has not resulted in a statistically significant overall survival difference.
- Providers have started to utilize and the guidelines have begun recommending consideration for choosing second generation agents based on patient risk scores. Bosutinib and ponatinib have not been approved in the front line setting at this point. However, they do both have potential roles in the second line treatment of CML.
- CML treatment decisions should be based on individual patient comorbidities, provider experience, continued response to initial treatment selection, and adverse event profiles.

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Abbreviations

The following abbreviations are used in this review:

CCyR	– complete cytogenetic response
CML	– chronic myelogenous leukemia
CP	– chronic phase
FISH	– fluorescent in situ hybridization
MHS	– Military Health System
NCCN	– National Comprehensive Cancer Network
NICE	– National Institute for Health and Care Excellence
OS	– overall survival
PCR	– polymerase chain reaction
Ph+	– Philadelphia chromosome positive
TKI	– tyrosine kinase inhibitors