Hematology/Oncology Pharmacy Association

HOPA News

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American Society of Hematology 2012 Annual Meeting: Meeting Highlights

Candice M. Wenzell, PharmD BCOP
Hematology/Oncology Clinical Pharmacist
Cleveland Clinic, Cleveland, OH

Introduction

The 54th annual American Society of Hematology (ASH) meeting took place in Atlanta, GA, December 8–11, 2012, with more than 20,000 people from all over the world in attendance. More than 3,000 poster presentations, 900 oral presentations, six plenary presentations, and many educational sessions were presented during the conference. Below are selected oral, poster, and plenary presentations from the meeting. Additional details on these studies and all abstracts can be found at www.hematology.org/Meetings/Annual-Meeting.

Acute Myeloid Leukemia

Abstracts 48 and 673: Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia

FMS-like tyrosine kinase 3 internal tandem duplications (FLT3-ITD) in patients with acute myeloid leukemia (AML) generally portend a poor prognosis. Quizartinib is an oral tyrosine kinase inhibitor that targets FLT3 and is effective in patients with ITD mutant and wild-type FLT3. Abstract 48 evaluated quizartinib in elderly patients 60 years of age and older. Of the 134 patients analyzed, 69% were FLT3-ITD positive, 31% were FLT3-ITD negative, and 1% had an unknown FLT3-ITD status. The starting dose ranged from 90 to 135 mg daily and was administered in a continuous fashion for 28-day cycles. The primary endpoint was composite complete remission (CRc), defined as complete remission (CR), complete remission with incomplete platelet recovery (CRp), or complete remission with incomplete hematologic recovery (CRi). The CRc rate in FLT3-ITD-positive patients was 54% (0% CR, 3% CRp, and 51% CRi) with a median duration of response of 12.7 weeks and an overall survival (OS) of 25.3 weeks. In FLT3-ITD negative patients, the CRc was 32% (2% CR, 2% CRp, and 27% CRi), with a median duration of response of 22.1 weeks and an OS of 19 weeks. This treatment served as a bridge to a potentially curative hematopoietic stem cell transplant in 8% of patients. Treatment-related adverse events occurring in more than 20% of patients were nausea, fatigue, anemia, QT interval prolongation, diarrhea, vomiting, dysgeusia, and febrile neutropenia. Grade 3 or 4 QT prolongation occurred in 13% of patients, and Torsade de Pointes occurred in one patient and was managed by dose modifications.

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Abstract 673 included patients who were treated with quizartinib after second-line, salvage chemotherapy or hematopoietic stem cell transplant. Of the 137 patients analyzed, 72% were FLT3-ITD positive, and 28% were FLT3-ITD negative. The starting dose ranged from 90 to 135 mg daily and was administered in a continuous fashion for 28-day cycles. The primary endpoint was also CRc. The CRc rate in FLT3-ITD positive patients was 44% (4% CR, 0% CRp, and 40% CRi) with a median duration of response of 11.3 weeks and an OS of 23.1 weeks. In FLT3-ITD negative patients, the CRc was 34% (3% CR, 3% CRp, and 29% CRi), with a median duration of response of 5 weeks and an OS of 25.6 weeks. This treatment served as a bridge to a potentially curative hematopoietic stem cell transplant in approximately 30% of patients. Treatment-related adverse events were similar to the cohort presented in abstract 48. Quizartinib is a promising treatment and is currently being evaluated in phase 1 and 2 studies as monotherapy and in combination with other agents.

Acute Promyelocytic Leukemia

Abstract 6: ATRA and Arsenic Trioxide (ATO) Versus ATRA and Idarubicin (AIDA) for Newly Diagnosed, Non High-Risk Acute Promyelocytic Leukemia (APL): Results of the Phase III, Prospective, Randomized, Intergroup APL0406 Study by the Italian-German Cooperative Groups Gimema-SAL-AMLSG

Tretinoin (ATRA) in combination with chemotherapy is often used as front-line treatment of patients with acute promyelocytic leukemia (APL), whereas arsenic trioxide (ATO) is generally reserved for patients at the time of relapse. This abstract was presented at the plenary session and revealed the results of a phase 3 study comparing ATRA and ATO to ATRA and chemotherapy as front-line treatment for 162 patients with non-high risk APL. Patients were randomized to receive treatment with ATRA and ATO alone (ATO 0.15/kg plus ATRA 45 mg/m^2 daily until CR, followed by ATO 5 days/week, 4 weeks on/4 weeks off, for a total of four courses and ATRA 2 weeks on/2 weeks off for a total of seven courses, previously described by Estey, et al. [Blood, 2006]) or ATRA and chemotherapy as previously published by Lo-Coco, et al. (Blood 2011). Of the 154 patients who were evaluated, the primary objective of EFS at 2 years was achieved in 97% of patients in the ATRA and ATO group and 86.7% in the ATRA and chemotherapy group. The CR rate was 97.4% and 100% in the ATRA and ATO group and ATRA and chemotherapy group, respectively. Fever and prolonged myelosuppression occurred significantly more often in the ATRA and chemotherapy arm. The authors concluded that the non-chemotherapy front-line regimen is at least not inferior to the standard chemotherapy-based regimen.

Acute Lymphoblastic Leukemia

Abstract 670: Anti-CD19 BiTE® Blinatumomab Induces High Complete Remission Rate and Prolongs Overall Survival in Adult Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)

Adults with relapsed/refractory precursor B-cell acute lymphoblastic leukemia (ALL) have poor outcomes, with only 35%–40% achieving a hematologic CR and a median OS of 4–6 months. Blinatumomab is a bispecific T-cell engaging (BiTE®) antibody that engages cytotoxic T-cells and redirects them toward CD19-expressing cells, causing T-cell mediated lysis of tumor cells. Adults with relapsed/refractory B-precursor ALL were eligible, and 36 patients were enrolled. Patients were treated with a continuous infusion of blinatumomab for 28 days followed by a 14-day resting period. An additional three cycles of blinatumomab or an allogenetic hematopoietic stem cell transplant (HSCT) were offered to those patients who responded to therapy. The primary endpoint was hematologic CR or CR with partial hematologic recovery (CRh) within two cycles, and it was achieved in 72% of patients, of which 38% had a CRh. Responses were more frequent in patients in first relapse (95%), compared with other patients (40%). Allogeneic HSCT was performed in 36% of patients with only one patient relapsing after HSCT at the time of the abstract submission. The median OS is 14.1 months for responders and 6.6 months in nonresponders. The most common adverse events that occurred in the extension cohort were pyrexia (70%), headache (39%), tremor (30%), and fatigue (30%). Cytokine release syndrome occurred in a few patients and was found to be effectively treated or

prevented by the use of dexamethasone. There is an ongoing global phase 2 study that is being conducted to confirm these results.

Chronic Myeloid Leukemia

Abstract 163: A Pivotal Phase 2 Trial of Ponatinib in Patients with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL) Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 12-Month Follow-Up of the PACE Trial

Although significant advances have been made for the treatment of chronic myeloid leukemia (CML), some patients still fail tyrosine kinase inhibitor (TKI) therapy, sometimes due to the development of a T315I mutation of BCR-ABL. Ponatinib is an oral, third-generation TKI that has optimal binding to the BCR-ABL active site and has activity against both native and mutant BCR-ABL, including T315I. This abstract discloses the 12-month results of the PACE trial. Patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to second-generation TKIs or with a T315I mutation were enrolled in this phase 2 trial. A total of 449 patients were enrolled, 203 with chronic phase (CP)-CML, 64 with CP-CML and the T315I mutation, 65 with accelerated phase (AP)-CML, 18 with AP-CML and the T315I mutation, 48 with blast phase (BP)-CML/Ph+ALL, 46 with BP-CML/Ph+ALL and the T315I mutation, and 5 with either CML or Ph+ALL without confirmation of the T315I mutation and who were not resistant or intolerant of second-generation TKIs but were still treated and evaluated in a safety analysis. The primary endpoint for patients with CP-CML was major cytogenetic response (MCyR) at any time within 12 months and was achieved in 50% of patients with CP-CML and 70% of patients with CP-CML and the T315I mutation. The primary endpoint for patients with AP-CML and BP-CML/Ph+ALL was major hematologic response (MaHR) at any time within 6 months and was achieved in 58% of patients with AP-CML, 50% of patients with AP-CML and the T315I mutation, 35% of patients with BP-CML/Ph+ALL, and 33% of patients with BP-CML/Ph+ALL and the T315I mutation. Response rates were found to be higher in patients exposed to less prior TKIs and those with a shorter duration of disease. The most common adverse events reported were thrombocytopenia, rash, and dry skin, all occurring in approximately 30% of patients. The most common serious adverse event was pancreatitis, occurring in 5% of patients, but was managed by dose modifications. Based upon the results of this study, ponatinib was recently FDA-approved for the treatment of CP, AP, and BP-CML and Ph+ALL that is resistant or intolerant to prior TKIs. A phase 3 trial comparing ponatinib to imatinib in newly diagnosed patients with CP-CML is ongoing.

Chronic Lymphocytic Leukemia

Abstract 189: The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Promotes High Response Rate, Durable Remissions, and Is Tolerable in Treatment Naïve (TN) and Relapsed or Refractory (RR) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Patients Including Patients with High-Risk (HR) Disease: New and Updated Results of 116 Patients in a Phase 1b/2 Study

BTK is an important mediator in the B-cell receptor signaling pathway in both normal and malignant B-cells and is overexpressed in CLL cells. Ibutinib is an oral TKI targeting BTK that inhibits B-cell activation and signaling. This abstract provides updated results of ibrutinib in patients with CLL/SLL. This was a phase 1b/2 study that enrolled 116 patients with relapsed/refractory CLL/SLL and elderly patients (≥ 65 years of age) with untreated CLL/SLL. All patients were given ibrutinib 420 mg or 840 mg orally daily. Safety was the primary objective of this study. The most common adverse events were diarrhea (54%), fatigue (29%), upper respiratory tract infection (29%), rash (28%), nausea (26%), and arthralgias (25%), and most were grade 2 or less. Only 6% of patients discontinued ibrutinib due to adverse events. There have been no long-term safety concerns identified. The overall response rate (CR + PR) was 71% in untreated patients (10% CR and 61% PR), 67% in relapsed/refractory patients (3% CR and 64% PR), and 50% in high-risk patients (0% CR and 50% PR). The estimated 22-month, progression-free survival (PFS) and OS is 96% and 96%, respectively, in untreated patients and 76% and 85%, respectively, in relapsed/refractory and high-risk patients.

Lymphoma

Abstract 798: Frontline Therapy with Brentuximab Vedotin Combined with ABVD or AVD in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma

Advanced stage Hodgkin lymphoma can generally be cured with a standard chemotherapy regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); unfortunately, up to 30% will still require salvage treatment. Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E, a microtubule-disrupting chemotherapy agent and is useful in patients with CD30 positive cancers, such as Hodgkin lymphoma.

This abstract reveals the results of this phase 1 study. Patients with advanced stage Hodgkin lymphoma were given brentuximab vedotin at doses of 0.6 (n = 6), 0.9 (n = 13), or 1.2 mg/kg (n = 6) with ABVD (standard doses) or 1.2 mg/kg (n = 26) with AVD (standard doses) administered on days 1 and 15 of a 28-day cycle for up to six cycles. Safety was the primary objective and no dose-limiting toxicities were observed in any of the combinations. The most common adverse events in the ABVD and AVD groups, respectively, were nausea (76%, 77%), neutropenia (80%, 69%), peripheral neuropathy (72%, 65%), vomiting (60%, 38%), fatigue (44%, 46%), and constipation (48%, 31%). The most common grade 3 or higher adverse events in the ABVD and AVD groups, respectively, were neutropenia (80%, 65%), anemia (20%, 12%), febrile neutropenia (20%, 8%), and pulmonary toxicity (24%, 0%). In the ABVD group, 44% of patients discontinued bleomycin due to pulmonary toxicity, interstitial lung disease, or pneumonitis. There was no pulmonary toxicity reported in the AVD group. As a result, brentuximab vedotin is not recommended to be administered in combination with bleomycin. There was a high complete response rate with both regimens—95% of patients in the ABVD group and 92% of patients in the AVD group. A phase 3 trial comparing ABVD and AVD plus brentuximab vedotin is ongoing.

Abstract 60: Brentuximab Vedotin Administered Concurrently with Multi-Agent Chemotherapy as Frontline Treatment of ALCL and Other CD30-Positive Mature T-Cell and N-Cell Lymphomas

Brentuximab vedotin is also useful in CD30-positive non-Hodgkin lymphomas (NHL), which are typically treated with anthracycline-containing chemotherapy regimens, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). This abstract presents the results of arm 2 of a phase 1 study of patients with CD30-positive NHL treated upfront with chemotherapy and brentuximab vedotin. Patients with higher-risk systemic anaplastic large cell lymphoma (sALCL) and other CD30-positive mature T- and NK-cell lymphomas were randomized to receive two cycles of brentuximab vedotin 1.8 mg/kg treatment every 3 weeks followed by six cycles of CHOP chemotherapy (standard doses) or up to six cycles of brentuximab vedotin 1.8 mg/kg in combination with standard-dose CHP chemotherapy (vincristine omitted due to overlapping neurotoxicity with brentuximab vedotin) every 3 weeks. Those patients who responded were given an additional 8–10 cycles of brentuximab vedotin monotherapy. Data from 26 of the 39 enrolled patients were presented, of which 19 had sALCL and seven had a mature T- or NK-cell lymphoma. The primary objective of this study was safety, and the maximum tolerated dose of brentuximab vedotin was not exceeded at 1.8 mg/kg with a dose-limiting toxicity (rash) occurring in only one patient. The most common adverse events were nausea (58%), fatigue (50%), diarrhea (50%), peripheral neuropathy (38%), and alopecia (38%). The most common adverse events grade 3 or higher were febrile neutropenia (19%), nausea (8%), neutropenia (8%), and pulmonary embolism (8%). Treatment was discontinued in 19% of patients due to adverse events, and brentuximab was dose-reduced to 1.2 mg/kg in 15% of patients. All patients achieved an objective response, of which 88% achieved a CR. A future phase 3 study comparing CHOP to brentuximab vedotin plus CHP is planned.

Myelodysplastic Syndrome

Abstract 421: Treatment with the Thrombopoietin (TPO)-Receptor Agonist Romiplostim in Thrombocytopenic Patients (Pts) with Low or Intermediate-1 (int-1) Risk Myelodysplastic Syndrome (MDS): Follow-Up AML and Survival Results of a Randomized, Double-Blind, Placebo (PBO)-Controlled Study

Thrombocytopenia occurs in approximately 50% of patients with low/intermediate-1 (Int-1) risk myelodysplastic syndrome (MDS) and is associated with a shortened OS; unfortunately, there are few therapeutic options available. Romiplostim is a thrombopoietin (TPO) receptor agonist that stimulates the production of platelets. Patients with low/Int-1 MDS with platelet counts $\leq 20 \times 10^9$/L or $\leq 50 \times 10^9$/L with a history of bleeding receiving supportive care were eligible for this phase 2 randomized, double-blind, placebo-controlled study. A total of 250 patients were randomized in a 2:1 fashion to receive weekly subcutaneous injections of romiplostim at a starting dose of 750 mcg, adjusted a maximum of 1,000 mcg or minimum of 250 mcg, or placebo for 26 weeks, followed by a 4-week interim wash-out period, a 24-week placebo-controlled extended treatment period, and a 4-week follow-up period. In February 2011, treatment with the study drug was stopped, and patients were moved to the long-term follow-up phase as instructed by the data-monitoring committee due to concerns of a potential risk for increased disease transformation to AML that outweighed the small potential benefit in bleeding reduction. At the time of the 2011 analysis, the incidence of increased peripheral blast counts to greater than 10% was 15% in the romiplostim-treated group and 3.6% in the placebo group, and the incidence of transformation to AML was 6% in the romiplostim-treated group and 2.4% in the placebo group (HR 2.51, 95% CI: 0.55, 11.47). The updated results include the long-term follow-up data as not all patients completed all follow-up at the time of the 2011 analysis. Since June 2011, two additional AML cases were reported in the placebo group, but were not recorded in time for the analysis in 2011. The updated 58-week incidence rate of transformation to AML was 6% in the romiplostim-treated group and 4.9% in the placebo group (HR 1.20, 95% CI: 0.38, 3.84). For data available to date (beyond 58 weeks), the OS was 38.3% in the romiplostim-treated group and 37.3% in the placebo group (HR 1.09, 95% CI: 0.71, 1.68). Transformation to AML beyond 58 weeks of follow-up was 8.9% in the romiplostim-treated group and 8.5% in the placebo group (HR 1.15, 95% CI: 0.47, 2.85). Safety concerns for transformation to AML are being further investigated.

Be a HOPA Volunteer

Volunteer for 2013–2014 Committees and Work Groups

Apply by April 30, 2013

Members interested in becoming involved in association activities or volunteering for one of the 2013–2014 committees or work groups can indicate their interest at the **HOPA Volunteer Activity Center** found on the HOPA website.

Visit this site to review current volunteer opportunities and to indicate your interest in participating on HOPA committees, work groups, or upcoming projects.

Volunteers can also provide a list of their skills and interests that the organization will use when seeking volunteers for future volunteer opportunities. Tell us how you would like to be more involved!

www.hoparx.org

Oncology Medication Safety Update: July–December 2012

Lisa M. Savage, PharmD BCOP BCPS
Specialty Practice Pharmacist, Medication Safety
The Arthur G. James Cancer Hospital and Solove Research Institute at The Ohio State University, Columbus, OH

High-profile events, drug shortages, and new governmental regulations have pushed medication safety to the forefront in many institutions. Several organizations publish medication safety information and materials. However, the task of sifting through this breadth of information can be a daunting one for the practitioner who is simply searching for oncology-related safety information.

This quarterly column will summarize some of the medication safety notifications released by the Institute for Safe Medication Practices (ISMP), the Food and Drug Administration (FDA), and other organizations. In addition to the *Medication Safety Alert!* newsletters, the ISMP also publishes *QuarterWatch*, a publication that monitors adverse drug events (ADEs) reported to the FDA by manufacturers, consumers, and healthcare professionals.[1] Although less than 1% of all serious ADEs are reported to the FDA[2], direct reporting from healthcare professionals and consumers (through the MedWatch program) often provides a unique perspective that may not be available in other reporting venues. *Serious ADEs* are defined as those that resulted in death, permanent disability, or birth defects; involved hospitalization or other intervention to prevent harm; were life-threatening; or involved other medically serious consequences.

This issue of *HOPA News* Oncology Medication Safety Update will cover July through December 2012.

Recalls, Withdrawals, and Safety Alerts from the FDA

- 10/6/12: The New England Compounding Centers (NECC) issued a recall of all products from its Framingham, MA, facility out of concern for contamination. As of 12/12/12, the FDA and CDC have identified bacterial and/or fungal contamination in unopened vials of betamethasone, cardioplegia, and triamcinolone solutions distributed and recalled from the NECC. While these drugs are not necessarily used in the oncology population, the situation heightens awareness surrounding compounding sterility and outsourcing. (www.fda.gov/Drugs/DrugSafety/FungalMeningitis/default.htm)
- 12/14/12: Three lots of carboplatin (Hospira) were voluntarily recalled in November 2012 due to visible particulates, later identified as carboplatin crystals. In December, further communication was released to the general public outlining the safety concerns in receiving drug-containing particulates. (www.fda.gov/Safety/Recalls/ucm332353.htm.)

Changes in Safety Labeling (See Details on FDA Website)

- **July 2012:** www.fda.gov/Safety/MedWatch/SafetyInformation/ucm314601.htm
  - 7/9/12: Risk Evaluation and Mitigations Strategy (REMS) approved for extended-release and long-acting opioids (www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm). Drugs affected by this ruling include morphine (Avinza, Kadian, MS Contin), buprenorphine (Butrans), methadone (Dolophine), hydromorphone (Exalgo, Palladone), oxymorphone (Opana ER), oxycodone (OxyContin), tapentadol (Nucynta), fentanyl (Duragesic), and combination products (Embeda—morphine/naltrexone).
  - Dexrazoxane, thyrotropin alfa, fulvestrant, leuprolide acetate, aldesleukin, abiraterone
- **August 2012:** www.fda.gov/Safety/MedWatch/SafetyInformation/ucm315860.htm
  - Cladribine, sorafenib, oxaliplatin, panitumumab
- **September 2012:** www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm323036.htm
  - Deferasirox, doxorubicin liposomal, paclitaxel protein-bound, denosumab, abiraterone
- **October 2012:** www.fda.gov/Safety/MedWatch/SafetyInformation/ucm326133.htm
  - Tocilizumab, pemetrexed, ipilimumab, pamidronate, bortezomib, rituximab, everolimus

  - Rituximab labeling changed to include a 90-minute infusion option for previously untreated follicular non-Hodgkin's lymphoma and diffuse large B-cell lymphoma patients who did not experience a grade 3 or 4 infusion-related adverse event during cycle 1 and are receiving a glucocorticoid-containing regimen.
- **November 2012:** www.fda.gov/Safety/MedWatch/SafetyInformation/ucm330881.htm
  - Pazopanib, ondansetron, romiplostim, sunitinib, zoledronic acid, lubiprostone
- **December 2012:** not available as of January 9, 2013

Drug Safety Communications from the FDA

- 12/4/12: **Update regarding 32 mg IV doses of ondansetron:** The 32 mg single IV dose of ondansetron will no longer be marketed because of the potential for serious cardiac adverse effects. The FDA is working with all manufacturers of premixed 32 mg doses to voluntarily recall them from the market through early 2013. Please see details on the FDA website for additional information (www.fda.gov/Drugs/DrugSafety/ucm330049.htm).

ISMP Medication Safety Alert!

- **September 6 (Volume 17, Issue 18):** Reports from several infusion centers to ISMP cite difficulty with the removal of romidepsin from the vial. The viscosity of the resultant solution yields approximately 1.6 to 1.8 ml of reconstituted drug to be withdrawn from the vial, which corresponds to 8 to 9 mg of the 5 mg/ml solution. This information is not mentioned in product labeling, on the Celgene website, or in typical drug information references, but it is contained in a letter sent by Celgene in response to a complaint or query (www.ismp.org/docs/Celgene_Istodax_romidepsin_letter.pdf).
- **September 30** was the deadline for the 2012 ISMP International Medication Safety Self-Assessment for Oncology. Your institution may already complete the Medication Safety Self-Assessment; however, this year was the first year for an oncology-specific version. The self-assessment focuses on 10 areas:
  - patient information
  - drug information
  - communication of drug orders and other drug information
  - drug labeling, packaging, and nomenclature
  - drug standardization, storage, and distribution
  - medication device acquisition, use, and monitoring
  - environmental factors, workflow, and staffing patterns
  - staff competency and education
  - patient education
  - quality processes and risk management.
- **October 4 (Volume 17, Issue 20)**
  - **QuarterWatch (2012, Q1):** Since 2008, the number of serious ADE reports received by the FDA has increased by 90%. Imatinib and erlotinib are two of the three drugs that have been attributed to the increase in reporting.
  - **Quarterly action agenda (QAA)** highlights a case where an alternative concentration of docetaxel was purchased; however, the concentration was not changed in the computerized physician order-entry system. The ISMP recommends implementing a protocol for addressing situations in which alternative concentrations are purchased. The QAA also highlights the similarities in labeling in Mylan's melphalan drug product and diluent.

Because HOPA members play different roles in the continuum of oncology care, the need for medication safety information will vary greatly. If you have any suggestions for future medication safety topics or comments on the contents of this issue, please provide feedback to *HOPA News* at info@hoparx.org, with "Medication Safety Column" in the subject line.

References

1. *ISMP Medication Safety Alert! Acute Care Edition.* May 31, 2012; 17(1):1-3.
2. Ahmad SR, Goetsch RA, Marks NS. Spontaneous reporting in the United States. In: Strom BL, ed. *Pharmacoepidemiology.* 4th ed. New York, NY: John Wiley & Sons; 2005:135-159.

Board Update

Lisa M. Holle, PharmD BCOP, HOPA President

Updated Strategic Plan

Periodically revisiting an organization's strategic plan to review progress, set priorities, and revise the plan if needed is a sound business practice. At the HOPA Board meeting in November, the HOPA Board and staff, under the facilitation of Paul Meyer of Tecker International, LLC, reviewed HOPA's strategic plan, which has been in effect for the past 2 years. Meyer was the facilitator during our strategic plan development and also has facilitated strategic plan developments with other large pharmacy organizations.

Some key revisions to the strategic plan include the following:

- Incorporate the HOPA Foundation's strategic plan goals and objectives into the overall HOPA strategic plan. At the time we developed our strategic plan, the Foundation had not yet been formed. It made sense to combine strategic plans at this time and ensure that HOPA's support of research is at the forefront of its organizational documents.
- The Research Goal was revised to read as follows: "HOPA supports research efforts of the hematology/oncology pharmacist to optimize the care of individuals affected by cancer." The objectives are as follows:
  - Provide grant funding to support research priorities focused on the practice of hematology/oncology pharmacy.
  - Increase the educational initiatives in research methodology training.
  - Increase the number of members actively engaged in research.
- The Education Goal's name was changed to the Professional Development Goal. This change will allow HOPA to continue to be recognized and used not only as an expert provider of hematology/oncology education, but also as professional development to support pharmacists involved in cancer care.
- The Professional Development objectives were revised to support updated goals and now are as follows:
  - Increase the breadth, quality, and quantity of HOPA's educational initiatives.
  - Increase opportunities for professional development of hematology/oncology pharmacists.
- The Advocacy Goal area objectives were revised to include new objectives that will continue to allow our advocacy efforts to grow, including the following:
  - Establish volunteer leadership infrastructure to sustain current knowledge to support the goal.
  - Increase member engagement in HOPA's advocacy initiatives.
  - Establish HOPA as a recognized stakeholder in oncology pharmacy practice issues such as quality, safety, and economics.
  - Increase patient and caregiver understanding of the role and value of the hematology/oncology pharmacist as an integral part of cancer care.
- The Standards Goal remained the same. The objectives, including the scope of practice and evidence-based guidelines, are ongoing.

I encourage each of you to review the updated strategic plan, which is available on the the HOPA website at www.hoparx.org/about/default/strategic-plan.html.

New HOPA Member Benefits

HOPA Bulletin

Beginning in January, HOPA members will be receiving a weekly *HOPA Bulletin* via e-mail that will provide brief summaries and links to articles about hematology/oncology pharmacy, cancer treatments, blood disorders, healthcare reform, and other issues found on the Internet or in the news, as well as current HOPA news. It is not intended to promote any type of practice but rather to provide information that may be of interest and that perhaps your patients and colleagues are reading.

Social Media

In December, HOPA created Facebook and LinkedIn pages. If you haven't already checked these out, please do. These forums will allow HOPA to be more visible to the public and provide members with an additional forum to communicate about hot topics and professional questions and learn about HOPA events, programming, and efforts. To reach these pages, visit the HOPA website, www.hoparx.org, and click on the links.

Health Policy Update

The Health Policy workgroups and committee have finalized issue briefs for our top advocacy agenda items, including

- role of the hematology/oncology pharmacist
- oral chemotherapy
- drug shortages
- biosimilars.

These issue briefs as well as recent advocacy items can be found on HOPA's Health Policy & Advocacy webpage: www.hoparx.org/Health-Policy/default/adv-activities.html. This page will be updated to reflect new health policy and advocacy information. If you would like to sign up to receive e-mail updates about health policy and advocacy information, please sign up at www.hoparx.org/maillist.html.

Upcoming HOPA Annual Conference

Join us in Los Angeles, CA, at the upcoming 9th Annual Conference, March 20–23, 2013. This year we will offer three preconference sessions, 6 hours of live BCOP sessions, 22 hours of live continuing education credit, special interest group discussions, symposia, corporate showcases, exhibits, poster sessions, and opportunities for networking with colleagues.

Preconference sessions include

- **Oncology 101 Boot Camp**, which will provide overviews of breast, lung, prostate, and colorectal cancer
- **BMT Boot Camp**, which will offer an introduction to hematopoietic stem cell transplantation (HSCT), graft-versus-host disease, and common infections that occur in patients undergoing HSCT, as well as more advanced information about HSCT
- **Research Workshop**, which will focus on the role of healthcare quality research in institutional and community practice settings and address the key elements and measureable endpoints for successful healthcare quality hematology/oncology pharmacy projects.

BCOP sessions include

- Updates in Cancer Screening and Prevention
- Current Treatment Strategies for Esophageal and Gastric Cancers
- Hodgkin's Lymphoma
- Multiple Myeloma Treatment Updates
- Updates on Treatment of Skin Cancers
- Beyond Chemotherapy: Psychosocial Care for the Cancer Patient.

John G. Kuhn Keynote Lecture

Our keynote speaker is Mark Pegram, MD, a renowned breast cancer researcher and director of the Breast Cancer Program at the Stanford Women's Cancer Center. His research focuses on the understanding of the molecular pathways that regulate HER2, and he is well-known for his landmark research that led to the development of trastuzumab.

Continuing Education Sessions

For the first time, we will be holding a session on current advocacy issues in Washington, DC, that affect pharmacists. We will also offer sessions addressing other hot topics, such as carboplatin dosing and oral oncology agents. Don't forget to also check out the breakout sessions for practical information about administrative, clinical, practice, and technical issues in oncology pharmacy practice.

We look forward to seeing you in Los Angeles!

Enzalutamide [Xtandi®]

Class: Androgen receptor signaling inhibitor

Indication: Metastatic castration-resistant prostate cancer (CRPC) patients who have previously received docetaxel

Dose: 160 mg orally once daily (four 40-mg capsules) with or without food

Dose modifications: For grade 3 or higher toxicity, hold doses for 1 week or until less than grade 2 toxicity. Consider a subsequent decrease to 80 mg or 120 mg daily. Decrease to 80 mg daily if administered with strong CYP2C8 inhibitor.

Common adverse effects: Fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache

Serious adverse effects: Seizures

Drug interactions: Substrate of CYP2C8 and CYP3A4. Avoid strong inducers of CYP3A4 and strong inducers and inhibitors of CYP2C8 if possible. Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Avoid narrow therapeutic index drugs that are metabolized by CYP3A4, CYP2C9, and CYP2C19.

Enzalutamide for Metastatic Castration-Resistant Prostate Cancer

Cara Burditt, PharmD
Stephanie Dunseith, PharmD
PGY2 Oncology Pharmacy Residents
University of Chicago Medical Center, Chicago, IL

With an estimated 241,740 new cases and 28,170 deaths in the United States in 2012, prostate cancer is the most common cancer in men aside from skin cancer.[1] Patients with advanced disease that has progressed despite surgical or medical castration are candidates for combined androgen blockade (CAB) with luteinizing hormone-releasing hormone (LHRH) agonist and antiandrogen therapy. Meta-analysis data suggest that CAB provides an incremental relative improvement in overall survival compared with LHRH agonists alone.[2] For patients who progress to symptomatic metastatic castration-resistant disease, first-line therapy with docetaxel and prednisone is offered. Once patients progress after docetaxel, there is no current consensus for the best additional therapy. CAB is one of many options, but the short-lived benefits may not outweigh the significant side effects.[3] There is a need for new therapeutic options for metastatic castration-resistant prostate cancer (CRPC) that progresses after docetaxel. Recent research findings have helped elucidate the biology of progressive disease, which is driven in part by overexpression of androgen-receptors. This overexpression confers resistance to conventional antiandrogen agents such as bicalutamide.[4] Given these findings, enzalutamide was developed based on its activity in prostate cancer models with overexpression of the androgen receptor.[5]

Enzalutamide is an androgen receptor-signaling inhibitor distinct from other antiandrogens in that it inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment.[6] It also differs from other antiandrogens due to its greater receptor affinity, ability to induce tumor shrinkage in xenograft models, and lack of known agonist effects.[5]

The AFFIRM trial, a multicenter, phase 3, double-blind, placebo-controlled study, randomly assigned 1,199 men in a 2:1 ratio to receive enzalutamide 160 mg daily or placebo. Patients were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status score and average pain score using the Brief Pain Inventory short form. All patients had a histologically or cytologically confirmed diagnosis of prostate cancer, with progressive disease despite castrate levels of testosterone and previous treatment with docetaxel. All patients continued androgen deprivation therapy for the duration of the study, and patients were allowed, but not required, to take glucocorticoids. Treatment with the study drug continued until radiographically confirmed disease progression. The primary endpoint of the study was overall survival (OS), and the secondary endpoints included radiographic progression-free survival (PFS), prostate-specific antigen (PSA) level, time to PSA progression, time to first skeletal-related event (SRE), and quality of life score. Results of the study showed a median OS of 18.4 months in enzalutamide-treated patients compared with 13.6 months in placebo-treated patients ($p < .001$). Enzalutamide was found to be superior to placebo for all secondary endpoints. There was a higher incidence of fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache in the enzalutamide-treated group. Additionally, five of the 800 (0.6%) enzalutamide-treated patients experienced a seizure during the study time period, while no seizures were noted in the placebo group. The results of the AFFIRM trial led to the FDA approval of enzalutamide for use in patients with metastatic CRPC progressing after treatment with docetaxel and prednisone.[5,7]

The most common side effects of enzalutamide observed in the AFFIRM trial were fatigue, back and musculoskeletal pain, diarrhea, hot flashes, headache, and peripheral edema.[4] The package insert for enzalutamide contains a warning for risk of seizures in patients taking enzalutamide. Seizures occurred in approximately 0.9% of patients treated with enzalutamide during clinical trials. Patients who experienced a seizure were permanently discontinued from enzalutamide therapy. Patients with a history of seizure or who were at an increased risk of seizures were excluded from the AFFIRM trial, and there is no trial data to date to offer guidance on the use of enzalutamide in these patient populations.[6]

Enzalutamide is supplied as 40-mg capsules, and is dosed at 160 mg (four capsules) orally once daily, without regard to food. Dosing modifications should be considered for patients who experience grade 3 or higher toxicity, or who are using concomitant strong CYP2C8 inhibitors. For patients who experience a grade 3 or higher toxicity, it

is recommended to hold doses of enzalutamide for at least 1 week or until symptoms resolve to ≤ grade 2, and then to resume at the same dose or a reduced dose of 80 mg or 120 mg daily if warranted. Enzalutamide is primarily eliminated by hepatic metabolism and is a substrate of CYP2C8 and CYP3A4. No dose modification is recommended for mild-moderate renal or hepatic impairment. Enzalutamide has not been studied in patients with severe renal or hepatic impairment.[6]

In addition to being a substrate of both CYP2C8 and CYP3A4, enzalutamide is also a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. The package labeling for enzalutamide recommends avoiding strong inducers and inhibitors of CYP2C8 and strong inducers of CYP3A4 during treatment with enzalutamide. If a strong inhibitor of CYP2C8 must be used, it is recommended to decrease the dose of enzalutamide to 80 mg daily. Narrow therapeutic index drugs that are metabolized by CYP3A4, CYP2C9, and CYP2C19 should also be avoided when possible. The maximum plasma concentrations of enzalutamide are reached 1 hour after dosing. Steady state is achieved by day 28, and the mean half-life is approximately 6 days.[6]

Patients should be counseled to take enzalutamide once daily, without regard to food. Patients who are receiving an LHRH analog should continue their treatment while receiving enzalutamide. Due to the increased risk of seizure associated with enzalutamide, patients should be counseled to avoid activities where a sudden loss of consciousness could cause serious harm to themselves or others and should be aware of conditions or medications that may predispose them to seizures. Enzalutamide may cause harm to a developing fetus, and it is recommended that both a condom and another effective method of birth control be used if a patient is having sex with a woman of reproductive potential while taking enzalutamide and for 3 months following treatment. A condom should also be used when having sex with pregnant females.[6]

Enzalutamide is one of three new therapies recently approved for metastatic CRPC. The NCCN guidelines have been updated to include enzalutamide as a treatment option in patients who have failed treatment with docetaxel. A phase 3 trial examining the use of enzalutamide in metastatic CRPC prior to treatment with docetaxel is currently under way, and a phase 2 trial comparing enzalutamide to bicalutamide in patients with disease progression after primary androgen deprivation therapy is currently recruiting subjects.[2,8] Enzalutamide offers a promising new therapy, and the results of upcoming research may expand its role in the treatment of advanced prostate cancer.

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Bosutinib (Bosulif®)

Class: Tyrosine kinase inhibitor

Indication: Adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy

Recommended dose: 500 mg orally once a day

Dose modifications

- In patients taking 500 mg per day with no grade ≥ 3 toxicity, increases to 600 mg per day can occur in patients with failure to achieve a satisfactory hematologic response by week 8 of treatment, or cytogenic response by week 12 of therapy
- Any hepatic impairment: 200 mg daily intial dose
- Elevations in liver transaminases
- Hematologic toxicity (ANC < 1,000 x 10^6/L or platelets < 50,000 x 10^6/L)
- Grade 3 or 4 diarrhea

Common adverse effects: Diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, pyrexia, fatigue

Serious adverse effects: Elevated lipase, hypophosphatemia, diarrhea, fluid retention, neutropenia, thrombocytopenia, elevated LFTs

Drug interactions: Strong or moderate CYP3A or P-gp inducers and inhibitors, acid suppressive agents (avoid PPIs, separate by antacids and H2 blockers by 2 hours)

Bosutinib: A New Orphan Drug Option for CML patients

Jessica M. Baron, PharmD
PGY1 Pharmacy Practice Resident
University of Massachusetts Memorial Medical Center, Worcester, MA

CML is diagnosed in more than 5,000 patients each year, with more than 95% of these patients carrying leukemic cells that display the Philadelphia chromosome (Ph).[1] This distinct genetic abnormality has become the target for agents utilized to treat CML patients. The treatment of CML with tyrosine kinase inhibitors (TKI) like imatinib have drastically improved the survival of patients with CML.[2] Bosutinib is the newest tyrosine kinase inhibitor to join imatinib, dasatinib, nilotinib, and ponatinib for the treatment of patients with CML.

Bosutinib differs from the other TKIs used in CML through its affinity for different genes and receptors. BCR-ABL is the hallmark genetic mutation of CML; its product is known as the Philadelphia chromosome. The rare cases of CML not caused by the BCR-ABL translocation are thought to be due to overexpression of SRC kinases.[3] The current TKIs utilized in CML treatment act by inhibiting the BCR-ABL mutation. However, bosutinib inhibits both BCR-ABL and SRC, allowing it to be considered a "dual" TKI. Bosutinib also has minimal activity against c-KIT and platelet-derived growth factor receptor, receptors implicated in the toxicity profile of the other TKIs, suggesting lower rates of myelosuppressive events with bosutinib.[4,7] Patients with the T315I mutation have not been shown to benefit from bosutinib.[4,5]

The trial earning bosutinib FDA approval, Study 200, was a phase 1/2, single-arm, open-label study performed to determine bosutinib's safety and efficacy in Ph+ CML or ALL with resistance or intolerance to prior TKI treatment. Utilizing the daily dose of 500 mg determined by the dose-finding phase of this trial, patients were separated into four groups: chronic phase (CP), accelerated phase (AP), blastic phase CML (BP), and Ph+ ALL treated with imatinib or imatinib followed by dasatinib, nilotinib, or both. Dose escalation to 600 mg was possible in patients with failure to achieve a satisfactory hematologic response by week 8 of treatment, or cytogenic response by week 12 of therapy. The primary outcome measure was major cytogenic response (MCyR) at week 24 in the CP CML cohort after displayed imatinib resistance only. Secondary outcomes included time of duration of MCyR, overall survival, progression-free survival rates at 1 and 2 years, and overall hematologic response.[6,7,8]

Interim results were reported at the American Society of Hematology (ASH) 2011 Annual Meeting. A total of 570 patients were enrolled. Of these patients, 200 patients were included in the primary endpoint analysis. At 24 weeks, MCyR rate was 33% (95% CI: [27-40]) in imatinib-resistant patients. PFS and OS at 2 years for both imatinib-resistant and intolerant patients were 79% and 92%, respectively. Bosutinib also showed potential benefit after other TKIs and in more advance phases of CML, although the study was not powered to look at these populations. Overall safety of all cohorts combined was reported. The most common adverse events were diarrhea (81%), nausea (41%), and vomiting (39%). The most common grade 3/4 nonhematologic lab abnormalities were hypermagnesemia (11%), increased ALT (8%), hypophosphatemia (7%), and increased lipase (6%). Hematologic grade 3/4 abnormalities varied in rate by stage of disease, but included thrombocytopenia (25% in primary cohort), neutropenia (19%), anemia (15%), and leucopenia (8%).[7,8]

Since the initial trial results, bosutinib has been studied in numerous trials attempting to receive approval for newly diagnosed CML patients and in solid tumor patients.[9] The BELA trial studied bosutinib versus imatinib in newly diagnosed patients with Ph+ CML. Rate of complete cytogenic response (CCyR), the primary endpoint, was not superior with bosutinib (70% versus 68%, $P = .601$). However, time to response (37.1 weeks versus 72.3 weeks, $P < .001$) and MMR at 12 months (41% versus 27%, $P < .001$) were statistically significant secondary endpoints favoring bosutinib. More grade 3/4 adverse events were seen with bosutinib compared to imatinib (64% versus 48%, $P < .001$), particularly diarrhea and vomiting. However, grade 3/4 neutropenia was less with bosutinib (11% versus 24%). Before the first follow-up,

31% of patients in the bosutinib arm discontinued the treatment, which may have contributed to the lack of superiority seen in this trial.[10]

Bosutinib has not shown benefit in solid tumor malignancies at this time. Two breast cancer studies terminated early for unfavorable benefit-risk ratios. Despite this, recruitment is ongoing for studies with bosutinib in recurrent glioblastoma and polycystic kidney disease.[9]

As this agent becomes integrated into CML treatment, providers should be aware of its specific counseling points. The medication should be taken with food, and LFTs and CBC should be monitored closely. The patient should be reminded to watch for signs and symptoms of jaundice or fluid retention (chest pain, shortness of breath, peripheral edema). A major point to keep in mind is the drug interaction profile of this medication, which includes medications that go through CYP3A4 or P-gp, or both, for metabolism and medications. Proton pump inhibitors should also be avoided, as they have been shown to decrease the Cmax by almost 50%. H2 blockers or antacids can be utilized if needed, but it is recommended that bosutinib be separated from them by at least 2 hours.[4]

Bosutinib provides a new option for Ph+ CML patients who have failed imatinib and dasatanib or nilotinib treatment. With its clear differences in both receptor affinity and side effect profile, it will be interesting to see whether this medication will eventually prove superior to the current TKIs for specific indications, or useful in other types of cancer.

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Tbo-filgrastim (Neutroval™)

Class: Recombinant human granulocyte colony stimulating factor (G-CSF)

Indication: Reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

Dose: 5 mcg/kg per day administered as a subcutaneous injection. The first dose should be administered no earlier than 24 hours following myelosupressive chemotherapy.

Dose modifications: None

Common adverse effects: The most common adverse effects included bone pain, asthenia, myalgia, headache, and diarrhea.

Serious adverse effects: The most common serious adverse effects include splenic rupture, acute respiratory distress syndrome, serious allergic reactions, sickle cell crises in patients with sickle cell disease, and the potential for tumor growth stimulatory effects on malignant cells.

Drug interactions: No formal drug interaction studies between tbo-filgrastim and other drugs have been performed.

Tbo-filgrastim: New Treatment for Cancer Patients with Sever Neutropenia

Meghan M. Devine, PharmD
PGY-2 Hematology and Oncology Specialty Resident
Wake Forest Baptist Health, Winston-Salem, NC

Neutropenia is defined as < 500 neutrophils/mcl or < 1,000 neutrophils/mcl and a predicted decline to ≤ 500/mcl over the next 48 hours. Febrile neutropenia is defined as neutropenia accompanied by a temperature of ≥ 38.3 °C orally or ≥ 38.0 °C over 1 hour that is induced by myelosupressive chemotherapy.[1] Febrile neutropenia is a major dose-limiting toxicity of chemotherapy and often requires prolonged hospitalization with broad-spectrum antibiotic use. The indication for prophylactic G-CSF use depends on the risk of febrile neutropenia or other neutropenic events that can potentially compromise treatment. The National Comprehensive Cancer Network (NCCN) guidelines recommend prophylactic G-CSF if the risk of febrile neutropenia is 20% or greater. Risk assessment is determined based on disease type, chemotherapy regimen, patient risk factors, and treatment intent. The American Society of Clinical Oncology and the European Organization for Research and Treatment of Cancer have both adopted the 20% threshold for considering routine prophylactic treatment. There is category 1 evidence to support filgrastim (Neupogen™) for the prevention of febrile neutropenia.[1] Natural human G-CSF, filgrastim, is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids. The first bacterially synthesized non-glycosylated recombinant methionyl form of human G-CSF was approved by the Food and Drug Administration (FDA) in 1991 under the generic name filgrastim. Tbo-filgrastim or XM02 is a biosimilar nonglycosylated G-CSF expressed in *Escherichia coli* that was clinically developed by BioGeneriX AG.[2] Tbo-filgrastim binds to G-CSF receptors and stimulates proliferation of neutrophils. G-CSF is known to stimulate differentiation commitment and some end-cell function activation, which increases neutrophil counts and activity.[3] Tbo-filgrastim was approved in an original biologics license application (BLA), which does not classify it as a biosimilar to filgrastim (Neupogen™) by the FDA. Tbo-filgrastim is not approved to be automatically substituted for Neupogen™. A biosimilar version of filgrastim, TevaGrastim®, is approved in Europe.

Tbo-filgrastim (XM02) safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer, lung cancer, and non-Hodgkin lymphoma. A total of 348 patients with breast cancer receiving docetaxel/doxorubicin chemotherapy were randomized with daily treatment injections (5 mcg/kg/day subcutaneously) for at least 5 days and a maximum of 14 days in each cycle. The primary endpoint was the duration of severe neutropenia in cycle 1. The mean duration of severe neutropenia was 1.1, 1.1, and 3.9 days in the XM02, filgrastim, and placebo group, respectively. Superiority of XM02 over placebo and equivalence of XM02 with filgrastim was demonstrated.[2] A total of 240 patients with small cell and non-small cell lung cancer receiving platinum-based chemotherapy were randomized in cycle 1 to treatment with daily injections (5 mcg/kg/day subcutaneously) for at least 5 days and a maximum of 14 days. The primary aim of this study was to show efficacy and safety of XM02 compared with filgrastim in the treatment of chemotherapy-induced neutropenia. The mean duration of severe neutropenia was 0.5 and 0.3 days in cycle 1 for XM02 and filgrastim, respectively. In the analysis of covariance for duration of severe neutropenia, the estimated treatment difference was 0.157 days, which was included in the prespecified equivalence range (-1, 1), illustrating no statistical difference.[4] A total of 92 patients with non-Hodgkin lymphoma receiving chemotherapy were randomized in cycle 1 to treatment with daily injections (5 mcg/kg/day subcutaneously) for at least 5 days and a maximum of 14 days. The mean duration of severe neutropenia was 0.5 and 0.9 days in cycle 1 for XM02 and filgrastim, respectively (P = .1055).[5] The most common adverse effects in all three trials included bone pain, fever, diarrhea, and headache. Rare but serious adverse events included splenic rupture, acute respiratory distress syndrome, allergic reactions, sickle cell crisis, and the potential for tumor growth stimulatory effects on malignant cells.[3] In the three trials discussed above, two were able to conclude that the adverse event profiles between filgrastim and tbo-filgrastim were similar.[4,5] The trial conducted by Giglio and colleagues concluded that the incidence of drug-related adverse effects across all cycles were seen more frequently in the filgrastim group (39.7%) than in the XM02 group (25.7%, P = .0149).[2] Important patient counseling points with this agent similar to filgrastim is that pain is common and can be treated with

acetaminophen or nonsteroidal anti-inflammatory medications as necessary. Patients should report the onset of pain in the left upper quadrant or left shoulder, as this may be a sign of rupture or enlargement of the spleen. Patients should report fever, dyspnea, rash, and urticaria immediately to their doctor. In patients with sickle cell disease, sickle cell crisis and death have occurred. The risk versus benefit in this population should be weighed prior to administration. If pregnancy occurs, patients should be advised of the possibility of fetal harm, because tbo-filgrastim is a pregnancy category C.[3]

Tbo-filgrastim is indicated to reduce the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosupressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The recommended dose is 5 mcg/kg/day administered subcutaneously. Recommended sites for subcutaneous injections include the abdomen (except for the 2-inch area around the navel), the front of the middle thighs, the upper outer areas of the buttocks, or the upper back portion of the upper arms. The injection site should be varied daily and should not be administered into an area that is tender, red, bruised, or hard or that has scars or stretch marks. No dose adjustment is recommended for patients with mild renal impairment (creatinine clearance 60–80 mL/min), and this drug has not been studied in patients with hepatic impairment. No formal drug interaction studies between tbo-filgrastim and other drugs have been performed. The first dose should be administered no earlier than 24 hours following myelosupressive chemotherapy and should not be administered within 24 hours prior to chemotherapy. Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. This product is available in single-use prefilled syringes that contain either 300 mcg or 480 mcg of tbo-filgrastim at a fill volume of 0.5 mL or 0.8 mL, respectively.[3] Teva Pharmaceutical Industries Ltd. announced that it does not expect to market tbo-filgrastim in the United States until November 2013 at the earliest.[6]

Tbo-filgrastim is not considered biosimilar to filgrastim by the FDA. Alternatively, TevaGrastim® is a biosimilar version of filgrastim approved in Europe. Tbo-filgrastim drug development began prior to the passing of the Biologics Price Competition and Innovation Act (BPCI) in March 2010. The BPCI now creates an abbreviated pathway for biologic agents to be approved. Although tbo-filgrastim is not considered a biosimilar, the development of the BPCI has made biosimilars a very popular topic in the global drug industry. Many pharmaceutical companies are teaming up to be involved in the development of biosimilars as they are expected to largely influence the drug development pipeline. Five of the top 15 drug expenditures for nonfederal hospitals are biologic agents including rituximab, pegfilgrastim, filgrastim, and trastuzumab.[7] Biosimilars are expected to allow for moderate cost savings and competition is likely to resemble brand to brand.

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Regorafenib (Stivarga®)

Class: Tyrosine kinase inhibitor: inhibits multiple kinases, including VEGF receptors 1-3, KIT, PDGFR-alpha and beta, RET, FGFR, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, SAPK2, PTK5, and Abl

Indication: Patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild-type, an anti-EGFR therapy

Dose: Regorafenib 160 mg (four 40 mg tablets) PO once daily with food (a low-fat breakfast), 21 days of every 28-day cycle, continued until disease progression or unacceptable toxicity

Dose modifications: Modify or hold doses based on toxicity: hand-foot skin reactions (HFSR), hypertension, liver function test elevations, any grade 3–4 adverse reaction

Common adverse effects: Asthenia/fatigue, decreased appetite and food intake, HFSR, diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia

Serious adverse effects: Hepatotoxicity, hemorrhage, severe HFSR, cardiac ischemia and infarction, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation or fistula, and wound healing complications

Drug interactions: Avoid concomitant use of strong inducers or inhibitors of CYP3A4 activity.

Regorafenib: A New Agent for Metastatic Colorectal Cancer

Tracy Reeb, PharmD
PGY2 Specialty Practice Resident, Hematology/Oncology
The Arthur G. James Cancer Hospital at The Ohio State University, Columbus, OH

In 2012, it is estimated that 143,000 men and women will be diagnosed with and almost 52,000 individuals will die of colorectal cancers.[1] Twenty percent of patients will be diagnosed with metastatic disease, and 50%–60% of patients initially diagnosed with nonmetastatic colorectal cancer will develop colorectal metastases.[1,2] Once metastases are present, colorectal cancer is associated with a 12% 5-year survival rate.[1] There are multiple initial treatment options available for patients with metastatic colorectal cancer containing combinations of 5-fluorouracil/leucovorin, capecitabine, irinotecan, oxaliplatin, bevacizumab, ziv-aflibercept, cetuximab, and panitumumab. However, treatment options become more limited after failing first- and second-line therapies.[2] On September 27, 2012, the U. S. Food and Drug Administration (FDA) approved regorafenib (Stivarga®) for patients with metastatic colorectal cancer that progresses in spite of standard first- and second-line therapies.

Regorafenib is an orally active bi-aryl urea multikinase inhibitor structurally related to sorafenib. Regorafenib is an inhibitor of VEGF 1-3, KIT, PDGFR-alpha and beta, RET, FGFR, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, SAPK2, PTK5, and Abl.[3] Regorafenib is unique in that it has more potent inhibition of VEGF-2, PDGFR-beta, FGFR-1, and c-Kit than sorafenib and possesses broader antiangiogenic properties through inhibition of TIE2.[4] Antitumor activity is exerted by inhibition of the angiogenesis, oncogenesis, and intracellular signaling mediated by these kinases.[3,4] With broad antitumor activity, regorafenib has been investigated in several solid tumor malignancies, such as renal cell carcinoma, hepatocellular carcinoma, metastatic colorectal cancer, and gastrointestinal stromal tumors (GIST).[4]

The original phase 1 dose-escalation study was conducted to assess the safety, pharmacodynamic, and efficacy profiles of regorafenib in patients with advanced solid tumors. Fifty-three patients were enrolled in several cohorts and received regorafenib doses ranging from 10 mg to 220 mg daily in differing schedules. Regorafenib 160 mg daily for 21 days of every 28-day cycle was determined to be the maximum tolerated dose, with the dose-limiting toxicities of hand-foot reactions (HFSR), hypertension, diarrhea, and rash/desquamation noted. Six percent of patients demonstrated a partial response to therapy, 60% had stable disease, and 23% had progressive disease with therapy. The most common tumor type enrolled, colorectal cancer, was identified to be of most interest for further analysis.[5] Based on these results, the trial was expanded to further evaluate the safety, tumor response, and progression-free survival (PFS) in patients with heavily pretreated metastatic colorectal cancer. Twenty-three additional patients enrolled in the extension phase received regorafenib 160 mg daily for 21 days of every 28-day cycle. The most common treatment-related adverse events were HFSR, fatigue, voice changes, anorexia, and diarrhea. Efficacy results were available in 28 patients. Partial response was achieved in one patient (4%), stable disease in 19 patients (70%), and progressive disease in seven patients (26%). Median PFS was 107 days (95% confidence interval [CI], 66–161).[6]

The impressive disease control rate of 74% (partial responses plus stable disease) in a patient population with limited treatment options led to the decision to proceed to a large international, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial. The CORRECT trial enrolled 760 patients with colorectal cancer who were unable to tolerate or failed standard therapy. Patients were randomized in a 2:1 fashion to receive regorafenib 160 mg daily for 21 days of every 28-day cycle (n = 505) or matching placebo (n = 255) until disease progression, unacceptable toxicity, or death. Baseline characteristics were well-matched, except patients in the regorafenib group were less likely to have a KRAS mutation (54% versus 62% in the placebo group) and had a higher proportion of patients who had progressed on bevacizumab, irinotecan, and oxaliplatin. Half of the patients had failed four or more previous therapies, all patients had previous anti-VEGF exposure, and very few patients had BRAF mutations (4% for regorafenib and 2% for placebo). The primary endpoint was overall survival; median overall survival for regorafenib was 6.4 months versus 5 months for placebo with a hazard ratio of 0.77 (95%

CI 0.64–0.94, $P = .0052$). Of note, an OS advantage was not found for KRAS mutated patients being treated with regorafenib, HR 0.87 (95% CI 0.64–1.17).

Secondary endpoints included PFS, objective tumor response, disease control rate, and safety. Patients treated with regorafenib had a median PFS of 1.9 months compared with 1.7 months for placebo, hazard ratio 0.49 (95% CI 0.42–0.58, $P < .0001$). This trend toward increased PFS with regorafenib remained true in patients with KRAS mutations (HR 0.53, 95% CI 0.43–0.65). No complete responses were achieved in either group, and partial responses accounted for only 1% of the patients in the regorafenib group and 0.4% of patients in the placebo group. The best response in either group was predominantly stable disease, and disease control rate (partial response plus stable disease) was higher in the regorafenib group (41% versus 15%, respectively). The most frequent adverse events (any grade, frequency ≥ 30%) in the regorafenib cohort were fatigue, HFSR, diarrhea, and anorexia. The most frequent grade 3–4 adverse events with regorafenib were HFSR, fatigue, diarrhea, hypertension, and rash/desquamation. Of note, 75.6% of patients receiving regorafenib required a dose modification, most of which were a result of an adverse event, and 70.4% of patients required dose interruptions. Dose interruptions lasting greater than 5 days were required in just more than half of the patients. The authors of this study concluded that regorafenib could be a new standard of care in late-stage metastatic colorectal cancer.[7]

Based on the results of studies evaluating regorafenib in metastatic colorectal cancer, the National Comprehensive Cancer Network has updated their guidelines regarding the treatment of colon and rectal cancers. Regorafenib is recommended as a treatment option after first, second, or third progression on therapies containing 5-fluorouracil/leucovorin, irinotecan, oxaliplatin, bevacizumab, and cetuximab or panitumumab if KRAS wild-type. Patients with mutant KRAS can be considered for regorafenib therapy in the second- or third-line setting and patients with wild-type KRAS in the third- or fourth-line setting.[2,8] Although regorafenib is a recommended therapy for metastatic colorectal cancer after failure of standard therapies, it is important to note that it comes at a starting cost of $9,350 per 28-day cycle. A recent editorial questions the cost-effectiveness of regorafenib therapy. The authors comment on the small incremental survival benefit, short PFS, and the potentially substantial adverse effects. They suggest that identification of the subset of patients most likely to derive significant clinical benefit from regorafenib therapy become a high priority.[9]

The most common adverse events (≥ 25%) associated with regorafenib reported in clinical trials are fatigue, HFSR, diarrhea, anorexia, voice changes, hypertension, oral mucositis, and rash/desquamation. Common grade 3–4 adverse reactions (≥ 5%) include HFSR, fatigue, diarrhea, hypertension, and rash/desquamation. The most serious adverse drug reactions are hepatoxicity (fatal in 0.3% of 1,100 patients), hemorrhage (21% overall incidence, fatal in 0.8%), and gastrointestinal perforation or fistula (0.6%), cardiac ischemia and infarction, reversible posterior leukoencephalopathy syndrome, and wound healing complications.[3] Laboratory abnormalities include elevated liver function tests (45%–65%), hyperbilirubinemia (45%), hypokalemia (9%), hypophosphatemia (6.4%), and hypocalcemia (6.4%).[3,7]

The manufacturer recommends dose modifications for HFSR, hypertension, liver function test elevations, and any grade 3–4 adverse reaction. Regorafenib therapy should be interrupted for any grade 3 HFSR (for a minimum of 7 days), grade 2 HFSR that are recurrent or unresponsive to dose reductions, symptomatic grade 2 hypertension, and any grade 3–4 adverse reaction. The dose of regorafenib should be reduced to 120 mg for grade 2 HFSR of any duration, after recovery from any grade 3–4 reaction, and for grade 3 elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The dose of regorafenib should be further reduced to 80 mg for recurrence of grade 2 HFSR at the 120 mg dose and after recovery of any grade 3–4 adverse reaction at the 120 mg dose (except hepatoxicity). Regorafenib should be permanently discontinued if the patient is unable to tolerate the 80 mg dose, for serious elevations in AST/ALT and bilirubin (see package insert for specifics), and for any grade 4 reactions. Empiric dose reductions for renal impairment and mild-moderate hepatic impairment are not required. Use is not recommended for patients with severe hepatic impairment.[3]

The bioavailability of regorafenib tablets is 69%, and absorption is dependent on the fat content of a meal. A high-fat meal increases the mean AUC (area under curve) of regorafenib by 48%, and a low-fat meal increases the AUC by 36%; regorafenib was administered with a low-fat meal in clinical studies. Regorafenib is metabolized by CYP3A4 and UGT1A9 to two active metabolites (M-2 and M-5). In vitro screening of CYP450 enzymes indicates that regorafenib and its metabolites competitively inhibit several CYP450 enzymes, making the potential for drug-drug interactions high. Regorafenib should not be administered with strong CYP3A4 inhibitors or inducers. Due to inhibition of UGT1A1 enzymes, regorafenib has the potential to interact with irinotecan. One study utilizing combination chemotherapy with regorafenib demonstrated a 28% increase in the AUC of irinotecan and a 44% increase in AUC of irinotecan's metabolite (SN-38).[3]

Regorafenib is only available through the REACH support program. For qualified patients, regorafenib is supplied as 40 mg tablets and is dispensed in packages containing three bottles of 28 tablets. Tablets should remain in the original bottle and not placed into pill boxes. Unused tablets should be disposed of 28 days after opening the bottle. These storage specifications may become confusing and problematic for patients when dose reductions and delays in therapy are required. Patients should be instructed to take four tablets (160 mg total) once a day with a low-fat breakfast that contains less than 30% fat. Examples of low-fat breakfast choices can be found in the package insert and at www.stivarga.com. Patients should be advised to monitor for signs and symptoms of severe HFSRs, diarrhea, hypertension, bleeding, and hepatoxicity. All patients of reproductive potential should be counseled on the need for effective contraception during and for up to 2 months after regorafenib therapy.[3]

Though currently only FDA approved for metastatic colorectal cancer, regorafenib has shown promising results in patients with GIST

and is being studied in other malignancies. A phase 3 study enrolled 199 patients with GIST refractory to imatinib and sunitinib. Patients were randomized to regorafenib 160 mg daily for 21 days of every 28-day cycle (n = 133) or placebo (n = 66). PFS was significantly improved with regorafenib (4.8 months) compared with placebo (0.9 months), hazard ratio 0.27 (95% CI 0.19–0.39, P < .0001).[10] Studies are currently being conducted to evaluate regorafenib in combination with FOLFIRI and mFOLFOX6 for colorectal cancer, in combination with pemetrexed and cisplatin for non-small cell lung cancer, and as a single agent for renal cell carcinoma, GIST, and hepatocellular carcinoma.[11] Studies further evaluating the potential for QTc prolongation, drug interactions (CYP2C8, CYP2C9, CYP3A4, and CYP2C19), and regorafenib pharmacokinetics in impaired renal function are also being conducted per request of the FDA.[12]

Key Issues

- Prior anti-VEGF therapy: 100% of patients in the CORRECT trial received prior bevacizumab therapy. Regorafenib, also an anti-VEGF therapy, was still able to demonstrate activity in this patient population.[7]
- Mutational status: Fewer patients in the regorafenib group had a known KRAS mutation. A benefit in PFS (HR 0.53, 95% CI 0.43–0.65) but not overall survival (OS; HR 0.87, 95% CI 0.67–1.12) was seen for KRAS mutant patients receiving regorafenib. Additionally, 96% of patients receiving regorafenib in the CORRECT trial were BRAF wild-type.[7]
- Dose reductions: A significant proportion of patients receiving regorafenib required dose modifications. The most frequent reasons for dose modifications were dermatologic, gastrointestinal, constitutional, and metabolic or laboratory events.[7]
- Ziv-aflibercept: Ziv-aflibercept was not an available treatment option for patients enrolled in the CORRECT trial. It is unknown what role regorafenib has after progression on ziv-aflibercept therapy.

Summary

- Regorafenib: Tyrosine kinase inhibitor with multiple targets including VEGF, cKIT, and BRAF currently indicated for treatment of metastatic colorectal cancer after progression on standard therapy (5FU, oxaliplatin, irinotecan, anti-VEGF therapy, and an anti-EGFR therapy if KRAS wild-type).[3]

Place in therapy: Currently, regorafenib provides an additional treatment option for heavily pretreated patients with metastatic colorectal cancer that have progressed through standard lines of therapy. The best response achieved by a majority of patients in clinical trials was stable disease, which resulted in a small but significant improvement in PFS and OS.[7]

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Omacetaxine Mepesuccinate [Synribo™]

Class: Protein synthesis inhibitor

Indication: Chronic or accelerated phase chronic myelogenous leukemia (CML) in patients with resistance or intolerance, or both, to two or more tyrosine kinase inhibitors

Dose: 1.25 mg/m^2 subcutaneous (SubQ) injection twice daily for 14 consecutive days of a 28-day cycle; continue until hematologic response is achieved

Maintenance: 1.25 mg/m^2 SubQ injection twice daily for 7 consecutive days of a 28-day cycle

Dose modifications: Hold and reduce the number of treatment days for hematologic toxicities, including grade 4 neutropenia or grade 3 thrombocytopenia.

Common adverse effects: Hyperglycemia, nausea, diarrhea, anemia, neutropenia, thrombocytopenia, fatigue, asthenia, pyrexia, infection, and injection-site reaction

Serious adverse effects: Acute coronary syndrome, cardiac dysrhythmia, gastrointestinal hemorrhage, neutropenia, thrombocytopenia, cerebral hemorrhage, and seizure

Drug interactions: No formal drug-drug interaction studies have been conducted.

Omacetaxine Mepesuccinate as an Anticancer Agent for Chronic Myelogenous Leukemia

Jennifer Kwon, PharmD
Hematology/Oncology Clinical Pharmacist
University of Washington Medical Center & Seattle Cancer Care Alliance
Seattle, WA

The cytogenetic hallmark of chronic myelogenous leukemia (CML) is the Philadelphia chromosome, which is the result of the reciprocal translocation between the breakpoint cluster region (BCR) gene on chromosome 22 and the Abelson (ABL) kinase gene on chromosome 9.[1] This results in the BCR-ABL fusion protein that includes an enzyme domain with abnormal tyrosine kinase catalytic activity, leading to uncontrolled cell proliferation and reduced apoptosis. The development of imatinib and related tyrosine kinase inhibitors (TKIs), which target the BCR-ABL region, has significantly improved therapeutic outcomes for most patients with CML. However, the emergence of drug resistance or intolerable side effects have hindered the success of TKIs in a reported 18% of CML patients.[2] In particular, the presence of an ABL mutation at position 315 (BCR-ABL T315I) does not respond to imatinib, the second generation TKIs (nilotinib and dasatinib), and the more potent TKI bosutinib. Until more recently, patients with the BCR-ABL T315I mutation had no effective therapeutic options available to them outside of a stem cell transplant.[3] The introduction of ponatinib in early December 2012 provided the first TKI active in CML patients with the T315I mutation.

Omacetaxine mepesuccinate is a first-in-class agent, which acts by different pathways than the TKIs, and is now another option for patients with T315I mutations. On October 26, 2012, the U.S. Food and Drug Administration (FDA) approved omacetaxine mepesuccinate for the treatment of patients with chronic or accelerated phase CML with resistance or intolerance to two or more TKIs.[4] Omacetaxine mepesuccinate is a reversible protein translation inhibitor that decreases intracellular levels of several antiapoptotic regulatory proteins.[5] The antileukemic effect of omacetaxine mepesucinate is not dependent on BCR-ABL and has activity against cells with T315I mutations.[6]

The accelerated approval of omacetaxine mepesuccinate was based on data from a combined cohort of patients in two open-label single-arm trials. The combined cohort included patients with CML-chronic phase (CML-CP) and CML-accelerated phase (CML-AP) who had previously been treated with two or more approved TKIs, to which they had shown resistance (e.g., via point mutations) or intolerance. All patients received omacetaxine mepesuccinate 1.25 mg/m^2 twice daily subcutaneously for 14 days every 28 days during the induction phase. After achieving a hematologic response, patients then were placed on a maintenance dosing schedule of omacetaxine mepesuccinate 1.25 mg/m^2 twice daily subcutaneously for 7 days every 28 days. Patients received at least one induction cycle of therapy prior to starting maintenance, and patients with no clinical response after six cycles of induction were removed from the study. The primary endpoints were major hematologic response (MaHR) and major cytogenetic response (MCyR). Secondary endpoints included degree of hematologic response, time to response, duration of response, progression-free survival (PFS), and overall survival (OS).[6,7]

A total of 76 patients with CML-CP and 35 patients with CML-AP were included in the efficacy analysis. For patients with CML-CP, 14 out of 76 patients (18.4%) achieved a major cytogenetic response after a mean of 3.5 months. The median duration of this response was 12.5 months. For those with CML-AP, 5 out of 35 patients (14.3%) achieved a major hematological response after a mean of 2.3 months, with a median duration of 4.7 months.[6-8]

The most common adverse reactions reported for at least 10% of patients were hematologic events, including thrombocytopenia, anemia, and neutropenia, and nonhematologic adverse events, including diarrhea, nausea, fatigue, fever, arthralgia, and injection-site reactions. There are no contraindications to administering omacetaxine mepesuccinate, but there are several precautions and warnings that should be noted. Fatalities related to myelosuppression occurred in 3% of patients in the safety population. Patients with neutropenia should be monitored frequently due to increased risk for infection. It is recommended to monitor complete blood counts (CBC) weekly during the induction and initial maintenance cycles, and every 2 weeks during the

later maintenance cycles. Omacetaxine can cause severe thrombocytopenia, as there was a high incidence of grade 3 and 4 thrombocytopenia (85% and 88%, respectively) in the clinical trials. Fatalities from cerebral hemorrhage occurred in 2% of patients in the safety population, and nonfatal gastrointestinal hemorrhages occurred in 2% of patients in the same population. Monitoring platelet count as part of the CBC is recommended. Avoiding anticoagulants, aspirin, and nonsteroidal anti-inflammatory drugs when the platelet count is less than 50,000/L is advised, as these agents may increase the risk of bleeding. Omacetaxine mepesuccinate can also induce glucose intolerance. Grade 3 or 4 hyperglycemia was reported in 11% of patients in the clinical studies. Patients with diabetes or risk factors for diabetes should have blood glucose levels monitored frequently. Omacetaxine mepesuccinate should not be given to patients with poorly controlled diabetes until good glycemic control has been achieved.[8]

Omacetaxine mepesuccinate caused embryo-fetal death in animal studies and should not be administered to pregnant women due to its potential to cause fetal harm. There are no well-controlled studies of omacetaxine mepesuccinate in pregnant women to show safety in this population. Females of reproductive potential should avoid becoming pregnant while undergoing treatment with omacetaxine.[8]

The recommended starting schedule of omacetaxine mepesuccinate for induction is 1.25 mg/m^2 administered subcutaneously twice daily for 14 consecutive days every 28 days. Cycles should be repeated every 28 days until patients achieve a hematologic response. The maintenance schedule for omacetaxine is 1.25 mg/m^2 administered subcutaneously twice daily for 7 consecutive days every 28 days. Patients should continue on maintenance therapy as long as they are getting clinical benefit from therapy. If a patient experiences grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 x 10^9/L) or Grade 3 thrombocytopenia (platelet counts less than 50 x 10^9/L) during a cycle, the next cycle should be delayed until ANC is greater or equal to 1.0 x 10^9/L and platelet count is greater than or equal to 50 x 10^9/L. The number of dosing days should also be reduced by 2 days (e.g., to 12 or 5 days) for the next cycle. Other clinically significant nonhematologic toxicities should be managed symptomatically by interrupting or delaying omacetaxine mepesuccinate until the toxicity has resolved.[8]

Omacetaxine mepesuccinate is absorbed following subcutaneous administration, achieving maximum concentrations after approximately 30 minutes. The plasma protein binding of omacetaxine mepesuccinate is less than or equal to 50%. It is primarily hydrolyzed to 4'-DMHHT via plasma esterases with minimal hepatic mediated metabolism in vitro, and is not a substrate of CYP450 enzymes. The potential for omacetaxine or 4'-DMHHT to induce CYP450 enzymes has not been determined. The major route of elimination of omacetaxine mepesuccinate is unknown. The mean percentage of the drug excreted unchanged in the urine is less than 15%, with the mean half-life following subcutaneous administration being approximately 6 hours. No formal pharmacokinetic studies have been conducted using omacetaxine mepesuccinate in patients with renal and hepatic impairment.[8,9]

Omacetaxine mepesuccinate is supplied as a 3.5 mg lyophilized powder in a single-use vial. Reconstitute each vial with 1 mL of 0.9% sodium chloride injection to create a 3.5 mg/mL solution. The lyophilized powder should completely dissolve in less than 1 minute to give a clear solution that should be protected from light. The reconstituted solution is stable for 12 hours at room temperature and 24 hours refrigerated.[8]

Omacetaxine mepesuccinate should be prepared and administered in a healthcare facility. Patients should be counseled on the possibility of serious bleeding due to low platelet counts and the likelihood that this drug will cause a decrease in white and red blood cells. Patients should notify their physician if they experience unusual bleeding or bruising, blood in the urine or stool, confusion, slurred speech, shortness of breath, significant fatigue, fever, or other symptoms of infection. Patients with diabetes should be advised of the possibility of hyperglycemia, and careful monitoring of blood glucose levels is warranted. Women of reproductive potential should use effective contraception measures to prevent pregnancy during treatment.

As a first-in-class agent, omacetaxine mepesuccinate provides a unique mechanism for fighting against CML. There are many cases where patients may not be able to continue treatment with TKIs due to resistance, intolerance, or disease progression. For these CML patients experiencing treatment failure with currently available TKI agents, omacetaxine mepesuccinate provides a new treatment option. With many advances in CML, new agents and new mechanisms offer new hope for patients diagnosed with CML, including those with a T315I mutation.

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