2017–2018 Drug Updates in Hematologic Malignancies

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Between 2016 and 2017, approval of several drugs by the US Food and Drug Administration (FDA), including four major drugs for acute myeloid leukemia (AML) and chimeric antigen receptor (CAR) T-cell therapy in acute lymphoblastic treatment (ALL), dramatically altered the landscape of treatment for hematologic malignancies; however, there were still gaps that needed to be covered. At JADPRO Live 2018, Rebecca J. Nelson, PharmD, BCOP, of Moffitt Cancer Center and Research Institute, discussed the pharmacology and indications of medications approved in the year 2017 to 2018 for the management of patients with hematologic malignancies and described the impact of these agents in advanced practice.

These approvals included monoclonal antibodies (moxetumomab pasudotox-tdfk [Lumoxiti] and mogamulizumab-kpkc [Poteligeo]) and CAR T-cell therapy (axicabtagene ciloleucel [Yescarta]). Dr. Nelson also covered expanded indications for pembrolizumab (Keytruda), tisagenlecleucel (Kymriah), blinatumomab (Blincyto), brentuximab vedotin (Adcetris), and obinutuzumab (Gazyva).

NEW DRUG: MOXETUMOMAB PASUDOTOX

Approved in September 2018, moxetumomab pasudotox is a CD22-directed antibody fused to a truncated bacterial toxin that inhibits protein synthesis and triggers apoptotic cell death. As Dr. Nelson reported, moxetumomab pasudotox is indicated for patients with relapsed or refractory hairy cell leukemia who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog. It is dosed at 0.04 mg/kg IV over 30 minutes on days 1, 3, and 5 every 28 days for up to 6 cycles, disease progression, or unacceptable toxicity.

Approval was based on data from a phase III, single-arm, open-label trial that showed an overall response rate of 75%, a complete response rate of 41%, and hematologic remission rate of 80% (Kreitman et al., 2018). In addition, approximately 30% of patients met the criteria for durable complete response (more than 180 days).

Nevertheless, Dr. Nelson noted some significant side effects. Grade 3 or 4 hypertension and febrile neutropenia adverse reactions occurred in more than 5% of patients, and grade 3

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or 4 capillary leak syndrome and hemolytic uremic syndrome were observed in nearly 4% of patients.

"It's very important to know about these side effects and educate our advanced practitioner staff about some of these toxicities," said Dr. Nelson, who also noted that infusion-related reactions occurred in up to 50% of patients and were seen throughout the treatment of this drug, not just in the first couple of cycles.

"Fluids are vitally important for patients on moxetumomab pasudotox," Dr. Nelson added. "These patients actually require 2 to 3 liters of fluids with each dose of drug and require fluid intermittently between days of treatment."

NEW DRUG: MOGAMULIZUMAB-KPKC

Mogamulizumab, a humanized IgG κ monoclonal antibody, is indicated for relapsed/refractory mycosis fungoides and Sézary syndrome after at least one systemic therapy. It is dosed at 1 mg/kg over 60 minutes weekly for 4 weeks, and then every subsequent cycle every 2 weeks.

Approval for mogamulizumab was based on data from the MAVORIC trial, which showed a 4-month improvement in progression-free survival vs. vorinostat (Zolinza; Kim et al., 2018). Improvement was seen for both mycosis fungoides (mostly grade 2 and 3) and Sézary syndrome, said Dr. Nelson, but it favored Sézary syndrome. The duration of response was also a bit longer in Sézary syndrome vs. mycosis fungoides.

According to Dr. Nelson, with a grade 4 rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis, mogamulizumab should be permanently discontinued. With grade 2 and 3 rash, treatment should be interrupted for 2 weeks and topical steroids applied.

As with any monoclonal antibody, infusion reactions can also occur, said Dr. Nelson, who noted that treatment should be discontinued for anaphylactic-type reactions. For temporary reactions, however, treatment can be restarted at lower doses following symptomatic care.

"Infusion-related reactions are very common," said Dr. Nelson, who noted that there was an over 90% incidence in the MAVORIC trial. "However, they are generally limited to the first couple of cycles. Premedication for infusion-related reactions is recommended."

EXPANDED INDICATION: PEMBROLIZUMAB

Based on data from the KEYNOTE-170 trial, indications for pembrolizumab were expanded to adult and pediatric patients with relapsed or refractory primary mediastinal large B-cell lymphoma (Zinani et al., 2017). In the multicenter, open-label, single-arm trial, patients were treated with pembrolizumab (200 mg IV every 3 weeks) until unacceptable toxicity or documented disease progression, or for up to 24 months or progression.

As Dr. Nelson reported, the trial demonstrated a 45% overall response, 11% complete response, and 34% partial response. Median duration of response was not reached within the follow-up period (median 9.7 months), and median time to first objective response was 2.8 months. According to Dr. Nelson, however, because of the delayed onset of action, pembrolizumab is not recommended for the treatment of patients with primary mediastinal large B-cell lymphoma who require urgent cytoreductive therapy.

Common adverse reactions to pembrolizumab include musculoskeletal pain, upper respiratory tract infection, pyrexia, fatigue, cough, dyspnea, diarrhea, abdominal pain, nausea, arrhythmia, and headaches.

EXPANDED INDICATION: BLINATUMOMAB

Based on data from the BLAST trial, blinatumomab now has an expanded indication for the treatment of adult patients and pediatric patients with B-cell ALL in their first or second complete remission with minimal residual disease (MRD) greater than 0.1% (Gökbuget et al., 2018).

"This is an important patient population because of the association between MRD-positive disease and a higher risk of relapse," said Dr. Nelson.

Patients in this open-label, multicenter, single-arm trial had received three chemotherapy lines prior to standard ALL therapy. After receiving their first cycle of blinatumomab, approximately 80% of patients became MRD-negative, said Dr. Nelson, who noted that these patients demonstrated a benefit in overall survival, hematologic relapse-free survival, and duration of hematologic remission.

EXPANDED INDICATION: BRENTUXIMAB VEDOTIN

As Dr. Nelson reported, brentuximab vedotin has expanded to two different indications. The first indication is for the treatment of adult patients with previously untreated stage III or IV classical Hodgkin lymphoma in combination with chemotherapy (Connors et al., 2018). Approval was based on ECHELON-1, a randomized, open-label, two-arm, multicenter trial (n = 1,334) that compared standard ABVD chemotherapy (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) to brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD). Patients were randomized to receive up to 6 cycles on days 1 and 15 of each 28-day cycle.

Important to note, said Dr. Nelson, was that patients randomized to the brentuximab arm demonstrated significantly better progression-free survival vs. standard ABVD. However, there was also increased toxicity, notably neutropenia and neuropathy.

"Brentuximab AVD is recommended for patients with stage III or IV disease who are unable to receive bleomycin," said Dr. Nelson. "Because of the increased neuropathy, however, patients with preexisting neuropathy should not be on this regimen."

Although there is clearly a progression-free survival difference, Dr. Nelson added, the cost of the medication should also be considered. The cost of brentuximab (along with an additional growth factor) is approximately $100,000 more than standard ABVD chemotherapy.

Brentuximab's other indication is for the treatment of adult patients with primary cutaneous anaplastic large cell and CD30-expressing mycosis fungoides who have received prior systemic therapy. Approval was based on the ALCANZA trial, a phase III, randomized, open-label, multicenter clinical trial of over 100 patients who received brentuximab compared to physician's choice of either methotrexate or bexarotene (Prince et al., 2017). Data showed a greater-than-10-month progression-free survival with brentuximab vs. methotrexate and bexarotene.

Adverse reactions were similar to those seen in the ECHELON-1 study, including primary or peripheral central neuropathy, diarrhea, fatigue, and again, neutropenia. The most common cause of discontinuation was peripheral neuropathy.

EXPANDED INDICATION: OBINUTUZUMAB

The FDA has also approved an expanded indication for obinutuzumab in adult patients with previously untreated stage II bulky, III, or IV follicular lymphoma. Approval was based on the GALLIUM trial, a multicenter, open-label, randomized phase III trial for patients with previously untreated non-Hodgkin lymphoma, including 1,202 patients with follicular lymphoma (Marcus et al., 2017). Patients were randomized to obinutuzumab plus chemotherapy or rituximab plus chemotherapy, followed in responding patients by obinutuzumab or rituximab (Rituxan) maintenance for up to 2 years.

While investigators observed longer progression-free survival in the obinutuzumab arm vs. rituximab arm, they did not see a difference in overall survival. The obinutuzumab arm also had a higher frequency of serious adverse events compared to the rituximab arm (50% vs. 43%), grade 3 or greater reactions (79% vs. 72%), and fatal infections (2% vs. less than 1%).

According to Dr. Nelson, oncologists remain divided over whether to substitute with either obinutuzumab or rituximab. Providers must weigh the benefit of progression-free survival against the risk of increased toxicity, said Dr. Nelson, who also noted concerns about the high cost of obinutuzumab.

NEW CAR T-CELL APPROVAL: AXICABTAGENE CILOLEUCEL

Chimeric antigen receptor (CAR) T cells are genetically modified T cells that target the patient's own tumor cells. In the case of both FDA-approved therapies, T cells are reprogrammed to identify and eliminate CD19-expressing malignant and normal cells.

Axicabtagene ciloleucel is approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma. Results of the

ZUMA-1 study showed sustained progression-free survival and overall survival in approximately 30% to 40% of patients (Neelapu et al., 2017). In patients who had partial response, however, response lasted only about 4 months, said Dr. Nelson.

Common grade 3 or higher adverse reactions include febrile neutropenia, fever, cytokine release syndrome (CRS), encephalopathy, infections, hypotension, and hypoxia. Serious adverse reactions occurred in 52% of patients and included CRS, neurologic toxicity, prolonged cytopenias (including neutropenia, thrombocytopenia, and anemia), and serious infections. Fatal cases of CRS and neurologic toxicity occurred.

"Because of the concern for fatal CRS, the FDA mandated that patients receiving treatment with axicabtagene ciloleucel undergo a Risk Evaluation and Mitigation Strategies (REMS) program," Dr. Nelson reported.

EXPANDED INDICATION: TISAGENLECLEUCEL

Based on data from the JULIET trial, which showed an overall response rate of 50%, a complete response rate of 32%, and median follow-up time of 9.4 months, the FDA has approved an expanded indication for tisagenlecleucel in patients with relapsed or refractory diffuse large B-cell lymphoma and diffuse large B-cell lymphoma after transformation from follicular lymphoma (Schuster et al., 2019). As Dr. Nelson reported, similar to the other CAR T-cell therapy, the duration of response was longer in patients with best overall complete response, as compared to best overall partial response. Common adverse events were almost identical to axicabtagene ciloleucel—CRS, infection risk, nausea, fatigue, hypotension—and a REMS program is also recommended by the FDA.

The big question, said Dr. Nelson, is which CAR T-cell therapy to use.

"They're both indicated for the exact same thing, and they both cost about the same amount of money," said Dr. Nelson. "The general consensus is that no one knows."

FDA APPROVALS: SMALL-MOLECULE INHIBITORS

New small-molecule inhibitors approved by the FDA included:

- Ivosidenib (Tibsovo) for the treatment of adult patients with relapsed or refractory AML with a susceptible *IDH1* mutation as detected by an FDA-approved test
- Acalabrutinib (Calquence) for the treatment of mantle cell lymphoma in patients who have received at least one prior line of therapy

The FDA approved expanded indications for these small-molecule inhibitors:

- Nilotinib (Tasigna): In two separate trials, patients who discontinued nilotinib after receiving it for 3 or more years did not progress to accelerated or blast phases of chronic myeloid leukemia (CML) during treatment-free remission
- Bosutinib (Bosulif) for the treatment of newly-diagnosed chronic-phase CML
- Dasatinib (Sprycel) for the treatment of pediatric patients with chronic-phase CML
- Venetoclax (Venclexta) for patients with chronic lymphocytic leukemia or small lymphocytic leukemia, with or without a 17p deletion, who have received at least 1 prior therapy

OTHER FDA APPROVALS

- Lusutrombopag (Mulpleta) was approved in July 2018 for thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure
- Methoxy polyethylene glycol-epoetin beta (Mircera) was approved in June 2018 for the treatment of pediatric patients 5 to 17 years of age on hemodialysis who are converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA
- Pegfilgrastim-jmdb (Fulphila) as a biosimilar for Neulasta (pegfilgrastim) in June 2018 to decrease the chance of infection associated with febrile neutropenia in patients with nonmyeloid cancer who are receiving myelosuppressive chemotherapy that has a clinically significant incidence of febrile neutropenia
- Avatrombopag (Doptelet) was approved by the FDA in May 2018 for the treatment of thrombocytopenia in adults with chronic liver disease scheduled to undergo a procedure

- Epoetin alfa-epbx (Retacrit) as a biosimilar to Epogen/Procrit (epoetin alfa) in May 2018 for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis and not on dialysis, use of zidovudine in patients with an HIV infection, and the effects of concomitant myelosuppressive chemotherapy. It is also approved for the reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery
- Fostamatinib disodium hexahydrate (Tavalisse) was FDA approved in April 2018 for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

Disclosure

Dr. Nelson has served on the speakers bureau and advisory board for BTG Inc.

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