2021–2022 Drug Updates in Hematologic Malignancies

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Presenter's disclosure of conflict of interest is found at the end of this article.

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Abstract

During JADPRO Live 2022, Jenni Tobin, PharmD, reviewed the indications of newly approved therapies in hematologic malignancies (including those for multiple myeloma, lymphoma, and acute leukemia) approved from late 2021 to late 2022. Dr. Tobin discussed their unique mechanisms of action, administration, and how to monitor for and manage side effects associated with these new therapeutics.

Leading up to JADPRO Live 2022, there were notable approvals from the US Food and Drug Administration (FDA) for therapeutics in hematologic malignancies, changing the treatment paradigms for malignancies such as multiple myeloma, lymphoma, and acute leukemia.

During the conference in Aurora, Colorado, Jenni Tobin, PharmD, of University of Colorado Cancer Center, Blood and Cellular Therapies Center, discussed the approved label indications and mechanisms of new drugs in hematologic malignancies. Dr. Tobin also discussed developing plans to monitor for and manage side effects associated with the administration of these newly approved drugs.

MULTIPLE MYELOMA: CILTACABTAGENE AUTOLEUCEL

Ciltacabtagene autoleucel (Carvykti; cilta-cel), a chimeric antigen receptor (CAR) T-cell therapy for the treatment of adults with relapsed and refractory multiple myeloma, is targeted against the B-cell maturation antigen, which is highly expressed in malignant plasma cells. This is the second CAR T-cell therapy for multiple myeloma, following the approval of idecabtagene vicleucel (ide-cel) last year.

Cilta-cel was studied in the CARTITUDE-1 trial, a phase Ib/II open-label study, which included patients with relapsed and refractory multiple myeloma who had received a median of six lines of therapy, and approximately 25% had high-risk cytogenetics (Berdeja et al., 2021). The primary outcome of the trial was the overall response rate, which was 97%, with a 67% stringent complete response and a third of patients being minimal residual disease negative.

"This response rate is more favorable than the 73% overall response rate reported with ide-cel,"

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said Dr. Tobin. "Additionally, the median duration of response was longer with cilta-cel when compared with ide-cel."

However, with the benefit of better response rates and longer duration of response, comes a trade-off in terms of toxicity. As Dr. Tobin reported, cilta-cel has a higher rate of toxicity compared with ide-cel. Almost 95% of patients had any-grade cytokine release syndrome, which typically occurred by day 7 after administration, unlike ide-cel where it typically occurs within the first 24 hours. Additionally, 5% of patients experienced a unique set of neurotoxicities that included late-onset neuromuscular- or neurocognitive-type side effects. Furthermore, the manufacturing failure rates were higher with cilta-cel when compared with ide-cel.

"Overall, cilta-cel provides another treatment option for patients with relapsed and refractory multiple myeloma who have failed four lines of therapy. It has a high chance of response and prolonged duration of response but a higher risk of toxicity," summarized Dr. Tobin.

DIFFUSE LARGE B-CELL LYMPHOMA: LONCASTUXIMAB

Loncastuximab (Zynlonta), an antibody-drug conjugate for the treatment of relapsed or refractory diffuse large B-cell lymphoma, was approved in April 2021. Loncastuximab is a targeted therapy that utilizes an antibody that binds to the CD19 protein, which is highly expressed in B-cell malignancies.

Loncastuximab was studied in the LOTIS-2 trial, a single-arm, multicenter phase II trial that included patients with relapsed or refractory diffuse large B-cell lymphoma who had failed at least two prior lines of therapy (Caimi et al., 2021). The primary endpoint of the trial was overall response rate, which was 48%. The median duration of response was 12.9 months, and median progression-free survival was 6.3 months.

Loncastuximab is administered at a dose of 0.15 mg/kg over 30 minutes every 21 days for the first two cycles, and then the doses drop to 0.075 mg/kg. Dexamethasone should be started (4 mg, administered intravenously or orally) and given the day before loncastuximab and continued for 3 days to prevent adverse events. It should be continued until progression or intolerability.

As Dr. Tobin reported, the most common adverse reactions were peripheral neuropathy, thrombocytopenia, neutropenia, anemia, and leukopenia.

"It is important to note that 9% of patients in the trial had received prior CD19-directed CAR T-cell therapy and that loncastuximab may have a different toxicity profile compared with other therapies," Dr. Tobin said. "As with any new therapy, health-care providers should weigh the potential benefits and risks for each individual patient before deciding on treatment."

"Overall, loncastuximab offers an additional treatment option for patients with relapsed or refractory large B-cell lymphoma who have failed previous treatments," she added.

ACUTE LEUKEMIA: ASPARAGINASE ERWINIA

In the leukemia space, two new agents were approved by the FDA: asparaginase erwinia chrysanthemi (recombinant)-rywn (Rylaze) and asciminib (Scemblix).

Asparaginase erwinia chrysanthemi is a recombinant form of asparaginase made from erwinia chrysanthemi. Asparaginase is an enzyme that cleaves asparagine, an essential amino acid necessary for cell growth, into aspartic acid and ammonia, thus depleting leukemic cells of their asparagine and inhibiting cell growth.

Asparaginase erwinia chrysanthemi is a new asparaginase product that addresses the short half-life and high levels of hypersensitivity and allergic reactions associated with previous asparaginase products derived from *E. coli*. It is dosed less frequently than other forms of asparaginase, said Dr. Tobin, but still has a short half-life, so it is usually administered on a Monday, Wednesday, Friday schedule.

CHRONIC LEUKEMIA: ASCIMINIB

Asciminib (Scemblix) was approved October 2021 for patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs). In addition, it was approved for patients with Ph+ CML in CP with the *T315I* mutation, which is a rare resistance mutation that affects 1% to 2% of CML patients. Asciminib is a selective inhibitor of

ABL1, a protein that plays a role in the development of CML and acute lymphoblastic leukemia (ALL; Hughes et al., 2019).

Asciminib was studied in the ASCEMBL trial, a phase III open-label randomized study for patients who had progressed after more than two lines of therapy or two lines of TKIs (Réa et al., 2021). The study found that asciminib was 12% more effective than bosutinib (Bosulif) in achieving major molecular response at week 24.

Dr. Tobin noted, however, that the significance of mutations at the ABL Myristoyl Pocket is not yet fully understood and is still being studied. In the ASCEMBL trial, 20 patients who had disease progression had a mutation in the ABL Myristoyl Pocket.

"Some patients who had a mutation, however, did not progress and were on asciminib for a year or more," she explained. "More research is needed to understand the clinical implications of this type of mutation."

The dosage of asciminib is 40 mg twice daily, but there are different dosings of the same drug. QT prolongation and arterial occlusive events are potential side effects, and it is recommended to monitor patients with a cardiovascular history.

Dr. Tobin also underscored potential drug interactions that may occur due to asciminib's interaction with CYP3A4, CYP2C9, or P-glycoprotein. It is recommended to consult with a pharmacist for further information on drug interactions, she said.

MYELOPROLIFERATIVE NEOPLASMS: ROPEGINTERFERON AND PACRITINIB

For the treatment of myeloproliferative neoplasms, there were approvals for ropeginterferon alfa-2b-njft (Besremi) and pacritinib (Vonjo).

Ropeginterferon is a pegylated form of interferon and is indicated for patients with polycythemia vera. It is dosed every 2 weeks, with most patients starting on 100 µg subcutaneously weekly. If the patient is on hydroxyurea, the starting dose is lower and can be titrated every 2 weeks up to a maximum of 500 µg.

According to Dr. Tobin, ropeginterferon may cause side effects such as myelosuppression, flu-like symptoms, muscle and joint aches, fevers, and psychiatric disorders such as depression and suicidality.

"It is recommended to take a small dose of aspirin prior to the first couple of doses," she said. "These symptoms usually subside after those first couple of doses. It is also important to avoid this medication in pregnant patients."

Pacritinib is FDA approved for adults with intermediate- or high-risk primary or secondary myelofibrosis who have a platelet count of less than 50,000/µL. This medication is important for this patient population because as thrombocytopenia worsens, said Dr. Tobin, the prognosis and overall survival decreases. Pacritinib is a JAK2 inhibitor that is JAK1 sparing and is thought to reduce thrombocytopenia and immunosuppression. It is dosed as 200 mg twice a day.

Pacritinib was studied in the phase III, multicenter PERSIST-2 trial, which had three treatment arms: pacritinib 400 mg once a day, pacritinib 200 mg twice a day, and best available therapy (Mascarenhas et al., 2018). The primary endpoints were greater than 35% reduction in spleen volume and greater than 50% reduction in total symptom score, both of which were more significant in the pacritinib arm.

Hematologic toxicities and non-hematologic toxicities such as diarrhea can occur with pacritinib treatment, and patients should be counseled about these potential side effects, said Dr. Tobin. Pacritinib does not cause a significant drop in platelet count from the initiation of therapy.

CHRONIC GRAFT-VS.-HOST DISEASE: BELUMOSUDIL

Finally, belumosudil is a ROCK (Rho-associated coiled-coil containing kinase) inhibitor used to treat adult and pediatric patients aged 12 and older with chronic graft-vs.-host disease (GvHD) who have failed two lines of prior systemic therapy.

According to Dr. Tobin, belumosudil works by reversing three key mechanisms that contribute to chronic GvHD: it inhibits ROCK2, decreasing activation of the STAT-3 pathway and downregulating T helper cells; it increases T regulatory cells to reduce alloreactivity; and it reduces the polymerization of actin component to decrease fibrosis.

Belumosudil is dosed at 200 mg by mouth once daily and is recommended to be taken with food. If the patient is on a proton pump inhibitor or a CYP3A4 inducer, however, the dose should

be increased to 200 mg orally twice a day, said Dr. Tobin.

Belumosudil was evaluated in the phase II, randomized, multicenter ROCKstar Study, which found that overall response rate between the once-daily and twice-daily dosing was similar, and that the median time to response was 5 weeks (Cutler et al., 2021). According to Dr. Tobin, however, the range of response was 4 to 66 weeks, "which means that it can take a while for the drug to start working." ●

Disclosure

Dr. Tobin has served as an advisor for ADC Therapeutics and Pharmacyclics, and has served on the speakers bureau for Karyopharm.

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