

2020–2021 Drug Updates in Hematologic Malignancies

PRESENTED BY KIROLLOS HANNA, PharmD, BCPS, BCOP

From M Health Fairview and Mayo Clinic College of Medicine, Maple Grove, Minnesota

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

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Abstract

During JADPRO Live Virtual 2021, Kirollos Hanna, PharmD, BCPS, BCOP, discussed the label indications of drugs and biologics in hematologic malignancies approved from late 2020 to late 2021, including mechanisms of action and various safety profiles so advanced practitioners can manage and treat patients safely with these new and approved therapeutic agents. In particular, CAR T-cell therapies were approved across many hematologic malignancies, along with PI3K inhibitors, anti-CD38 monoclonal antibodies, and immunotherapies.

With multiple new approvals and new indications, 2021 was the year of CAR T-cell therapies in hematologic malignancies. Joining the list of approvals were PI3K inhibitors, anti-CD38 monoclonal antibodies, and expanded indications for immunotherapy.

During JADPRO Live Virtual 2021, Kirollos Hanna, PharmD, BCPS, BCOP, of M Health Fairview and Mayo Clinic College of Medicine, reviewed the approved label indications of new drugs and biologics in oncology and discussed the adverse events associated with the administration these agents.

CAR T-CELL THERAPIES

Axicabtagene ciloleucel (Yescarta), an anti-CD19-CD28-CD3z construct, was approved in adults with relapsed/refractory large B-cell lym-

phomas who had received at least two lines of therapy based on results of the phase II ZUMA-1 trial, which demonstrated an overall response rate of 82% and a complete response rate of 54% (Neelapu et al., 2017). In 2021, FDA granted accelerated approval to axicabtagene ciloleucel for relapsed or refractory follicular lymphoma after at least two lines of systemic therapy (Locke et al., 2019).

Lisocabtagene maraleucel (Breyanzi), an anti-CD19-41BB-CD3z construct, was also approved for large B-cell lymphomas in the relapsed/refractory setting. Approval was granted based on results of the TRANSCEND NHL 001 trial that showed a 73% overall response rate, including complete responses in 53% of patients (Abramson et al., 2020). Indications for lisocabtagene maraleucel include diffuse large B-cell lymphoma (DLBCL) not otherwise

specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

Tisagenlecleucel (Kymriah), an anti-CD19-41BB-CD3z construct, was approved for various B-cell precursor acute lymphocytic leukemia (ALL) in patients up to age 25 and in relapsed/refractory B-cell lymphomas after at least two prior lines of therapy. Approval was based on results of the JULIET trial, which showed a 52% response rate, including complete responses in 54% of patients (Schuster et al., 2019).

Finally, brexucabtagene autoleucel (Tecartus), an anti-CD19-CD28-CD3z construct, was approved for patients with relapsed/refractory mantle cell lymphoma based on results of the ZUMA-2 study, which showed a 93% response rate, including complete responses in 67% of patients (Wang et al., 2020).

“This was a heavily pretreated population of patients with an aggressive lymphoma, so a response rate of 93% is very impressive and not something that’s seen with current approved therapies, especially in patients who have progressed on four or five lines of therapy,” said Dr. Hanna. “Median progression-free survival was also not reached at data cutoff, which again, is very promising for these patients.”

The most common (≥ 10%) grade 3 or higher reactions on brexucabtagene autoleucel were anemia, neutropenia, thrombocytopenia, hypotension, hypophosphatemia, encephalopathy, leukopenia, hypoxia, pyrexia, hyponatremia, hy-

pertension, infection—pathogen unspecified, pneumonia, hypocalcemia, and lymphopenia. There are also Risk Evaluation and Mitigation Strategies (REMS) protocols in place for cytokine release syndrome (CRS) and neurologic toxicities.

“Mantle cell lymphoma has seen really exciting updates this year,” said Dr. Hanna, who noted that many of these patients may be candidates for autologous stem cell rescue, BTK inhibitors, PI3K inhibitors, and various other combinations. “We now have CD19-targeted CAR T-cell therapies to add to the list” (Table 1).

BELANTAMAB MAFODOTIN

Belantamab mafodotin (Blenrep), an antibody-drug conjugate that targets the B-cell maturation antigen (BCMA), was another notable drug approved in the past year. Approval was based on the open-label, randomized phase II DREAMM-2 trial in relapsed/refractory multiple myeloma patients after three or more prior lines of therapy and who were refractory to immunomodulatory drugs, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (Lonial et al., 2020).

Patients on study were dosed with two different strategies but benefited from belantamab mafodotin regardless of dosing, with response rates between 31% and 34%.

Ocular toxicities were common with belantamab mafodotin, with 72% of patients experiencing keratopathy (Farooq et al., 2020). With dose holds, however, Dr. Hanna noted that most patients recover from keratopathy and visual changes. Moreover, 88% of patients maintained or

Table 1. FDA-Approved CD19-Targeted CAR T-Cell Therapies

Axicabtagene ciloleucel	Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from follicular lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma
Brexucabtagene autoleucel	Adults with R/R MCL
Lisocabtagene maraleucel	Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B
Tisagenlecleucel	Patients aged up to 25 years with B-cell precursor ALL that is refractory or in second or later relapse Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma

Note. ALL = acute lymphoblastic leukemia; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; NOS = not otherwise specified; R/R = relapsed/refractory. Information from Kite Pharma, Inc. (2021a, b); Novartis Pharmaceuticals Corporation (2021).

deepened response with dose holds more than 63 days, and keratopathy only to discontinuation of treatment in 3% of patients.

“If ophthalmology is not a specialty readily available within your building or within your clinic, these adverse events can be a challenge,” said Dr. Hanna, who noted that an ophthalmology evaluation is required prior to each dose of belantamab per REMS program. “Although manageable, the keratopathies are quite profound.”

UMBRALISIB

Accelerated approval of umbralisib (Ukoniq), a next-generation inhibitor of PI3K with improved selectivity, was based on analysis of the UNITY-NHL trial, which analyzed umbralisib monotherapy in indolent non-Hodgkin lymphoma (Zinzani et al., 2020). In the overall patient population, umbralisib monotherapy yield a 47.1% overall response rate and an 81.3% disease control rate.

With respect to adverse events, Dr. Hanna noted that any type of inflammatory process can manifest on umbralisib, and autoimmune side effects may require steroids in addition to holding therapy. Because of improved selectivity, however, umbralisib may be associated with decreased off-targeted kinase activity leading to fewer autoimmune events.

Umbralisib was approved by the FDA for marginal zone lymphoma after at least 1 prior anti-CD20-based regimen and follicular lymphoma after at least 3 prior lines of systemic therapy.

“In marginal zone lymphoma, we do not have many options that demonstrate significantly better outcomes utilizing BTK inhibition vs. PI3K, but in follicular lymphoma, we have many more therapeutic options,” said Dr. Hanna.

IDECABTAGENE VICLEUCEL

Another CAR T-cell product, idecabtagene vicleucel (Abecma) was approved for patients with relapsed/refractory multiple myeloma who were refractory to at least three prior regimens, including immunomodulatory drugs, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. With 25 months follow-up, results of the KarMMa trial showed a response rate of approximately 50% based on various dosing strategies, and one in five patients achieved a complete response or a stringent complete response (Munshi et al., 2021).

“Targeting BCMA is becoming more and more popular in the myeloma patient population,” said Dr. Hanna, who noted that both idecabtagene vicleucel and belantamab target BCMA.

As with most CAR T-cell therapies, cytokine release syndrome (CRS) is a common adverse event with idecabtagene vicleucel. Although more than 80% of patients experienced at least one CRS event on study, however, Dr. Hanna reported a low incidence of grade 3 or 4 adverse events. The median onset of CRS was approximately 1 day.

“We do have to be cognizant of [the potential for rapid onset] when we administer these cells, but it’s very good that we tend to see a very quick resolution for patients,” said Dr. Hanna, who noted that the median duration of CRS was between 4 and 6 days.

In addition, 18% of patients treated with idecabtagene vicleucel experienced neurotoxicity. All events occurred within 1 week of CRS, said Dr. Hanna, who noted that neurotoxicities also resolved within 6 days on average.

ADDITIONAL APPROVALS

The combination of carfilzomib and daratumumab with dexamethasone was also approved for multiple myeloma following one to three prior lines of therapy. Results of the CANDOR trial demonstrated an 81% response rate, with a duration of response of 27.5 months (Dimopoulos et al., 2020).

“Daratumumab now has a subcutaneous formulation that has really optimized how it’s used in the clinical setting,” said Dr. Hanna. “We implement a 3.5-hour observation time for the first dose of subcutaneous daratumumab, and nothing for subsequent doses. We’ve seen no increased incidence of safety events utilizing that specific approach.”

Tafasitamab-cxix (Monjuvi), a CD19 monoclonal antibody, was approved in combination with lenalidomide for adults with DLBCL ineligible for transplant. Results of the L-MIND study demonstrated an overall response rate of 55%, including complete responses in 37% of patients (Salles et al., 2020). Median response duration was 21.7 months.

“Historically, therapeutic options for this patient population have been limited by age, performance status, and comorbidities,” said Dr. Hanna. “This combination gives us a more intensive option, which is a very good development.”

“It’s becoming increasingly challenging to know the best option to manage our patients with multiple myeloma once they progress on three or more lines of therapy,” said Dr. Hanna. “Thankfully, the NCCN has done a great job breaking down the treatment guidelines in the relapsed/refractory setting to identify the most appropriate regimen for every patient.”

FUTURE DEVELOPMENTS

According to Dr. Hanna, the future treatment landscape of multiple myeloma in the next year or two will see an increased use of combination therapies.

“When daratumumab was first FDA approved, it was after four prior lines of therapy as monotherapy, but now, it’s moved all the way to front-line patient management in combination with other therapies that we have already been using,” said Dr. Hanna. “In multiple myeloma, we will continue to see BCMA-targeted agents studied in combination with other active agents, such as immunomodulatory drugs and proteasome inhibitors, and these therapeutic options will continue to move up the treatment landscape.”

“Treatment selection for our patients will become increasingly challenging,” he concluded. ●

Disclosure

Dr. Hanna reported financial relationships with AbbVie, Amgen, Astellas Pharma, Inc., Bristol Myers Squibb, and Seattle Genetics.

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