Successful Management of Patients Receiving Bispecific Antibodies for Hematologic Malignancies

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Abstract

As more bispecific antibody therapies are approved, advanced practitioners must be aware of their unique dosing strategies, toxicity profiles, and patient monitoring and coordination requirements. At JADPRO Live 2024, presenters discussed the management of patients receiving bispecific antibodies for hematologic malignancies, highlighting step-up dosing protocols, adverse effects, and the importance of patient education and monitoring.

Bispecific antibodies have revolutionized the treatment of hematologic malignancies, but their successful management requires a coordinated approach. At JADPRO Live 2024, Zahra Mahmoudjafari, PharmD, MBA, BCOP, FHOPA, Clinical Pharmacy Manager in the Division of Hematologic Malignancies & Cellular Therapeutics at the University of Kansas Cancer Center, and Jill O'Brien, Physician Assistant at the Cleveland Clinic, discussed emerging trends, operational considerations, and the role of advanced practitioners in optimizing patient outcomes.

MECHANISM OF ACTION

"Bispecific antibodies have two distinct antigen-binding sites that exert multiple mechanisms of action at the same time," Dr. Mahmoudjafari said.

Most approved bispecifics target CD3 on T cells and a specific tumor antigen on cancer cells. This dual engagement leads to immune-mediated tumor destruction through immune cell recruitment, leading to tumor cell death via perforins and granzymes, interference with receptor signaling, and expansion of T cells, and therefore enhanced immune response (Figure 1) .

Currently, there are nine approved bispecific antibodies. T-cell engagers dually target CD3 and the following: CD19 (blinatumomab, Blincyto), CD20 (mosunetuzumab, Lunsumio; glofitamab, Columvi; and epcoritamab, Epkinly), BCMA (teclistamab, Tecvayli; elranatamab,

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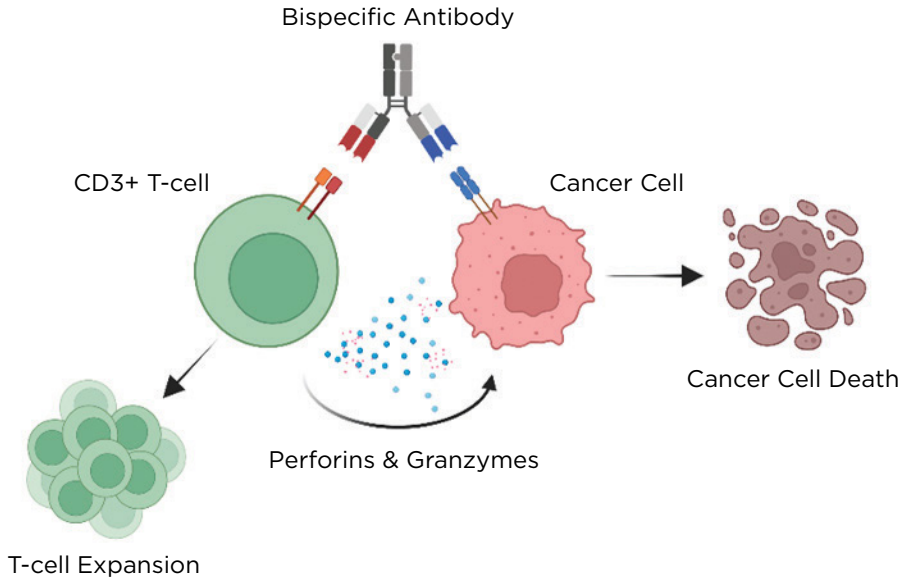

Figure 1. Bispecific antibody. Klein et al. (2024). Image created by BioRender.

Elrexfio; and linvoseltamab), GPRC5D (talquetamab, Talvey), and DLL3 (tarlatamab, Imdelltra).

"There has been significant advancement over what I consider a short period of time," Dr. Mahmoudjafari commented.

BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA

Sequencing Treatment

Multiple myeloma is a hematologic malignancy characterized by plasma cell proliferation, leading to bone disease, anemia, and renal dysfunction. There is currently no universal standard for sequencing treatments in multiple myeloma due to the rapid evolution of therapeutic options. Recommendations exist for both early and later relapse, but the landscape is still shifting. As of now, bispecific antibodies are primarily used in patients who have undergone at least four prior lines of therapy, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory drug (IMiD). Given the changes in frontline treatment strategies, nearly all multiple myeloma patients now receive anti-CD38 therapy early in their treatment course. CAR T-cell therapy, which was initially used in later lines, has also moved up in the treatment paradigm.

"It is important to keep the entire patient in mind when making decisions. You should be considering all treatment options at the time of diagnosis," Dr. Mahmoudjafari emphasized.

When making treatment decisions, providers must consider the patient's overall condition, including comorbidities, prior treatments, and risk factors for disease progression. High-risk features such as cytogenetic abnormalities, high-risk gene expression profiling, extramedullary disease, and the presence of circulating plasma cells can influence treatment strategies. Early relapse within 18 to 24 months of treatment is a strong predictor of poor prognosis, necessitating a more aggressive approach. Other factors include frailty, access to treatment centers, and personal treatment goals.

Those with relapsed/refractory disease who have undergone more than four prior lines of therapy are recommended to receive bispecific antibodies, including teclistamab (Tecvayli), elranatamab (Elrexfio), and talquetamab (Talvey).

Bispecific Therapies

Two bispecific antibodies targeting BCMA are teclistamab and elranatamab. The MajesTEC-1 trial demonstrated a 66% real-world response rate for teclistamab, even in heavily pretreated

patients. The MagnetisMM-3 trial showed a 61% response rate for elranatamab.

For teclistamab, the step-up dosing schedule typically occurs on days 1, 4, and 7, although some institutions may administer doses on days 1, 3, and 5 to minimize hospitalization duration. After the step-up phase, teclistamab is administered at a final dose of 1.5 mg/kg once weekly. The package insert recommends hospitalization for 48 hours following each of the first three doses to monitor for cytokine release syndrome (CRS) and other immune-related toxicities.

Elranatamab has step-up doses on days 1 and 4. The standard dosing regimen consists of 12 mg subcutaneously on day 1, followed by 32 mg on day 4, and continued 32 mg maintenance doses. Hospitalization is recommended for at least 48 hours after the first dose and 24 hours after the second dose.

A newer bispecific antibody, talquetamab, targets GPRC5D rather than BCMA. GPRC5D is expressed in keratinized tissues, leading to a different side effect profile compared to BCMA-targeted therapies. The MonumenTAL-1 trial explored both weekly and biweekly dosing schedules for talquetamab, with the biweekly regimen showing a 64% overall response rate.

The dosing schedule for talquetamab involves step-up doses on days 1, 4, 7, and 10, with hospitalization recommended for 48 hours following each of these doses. Most treatment centers are opting for the biweekly schedule to reduce treatment burden while maintaining efficacy.

Emerging Trends

Recent research has explored using bispecific antibodies, such as talquetamab, as a bridging therapy before CAR T-cell therapy. Outpatient administration of bispecific antibodies is another area of focus. Bispecific antibodies are also being studied in combination with other agents to determine whether they can enhance efficacy while maintaining manageable toxicity profiles.

BISPECIFIC ANTIBODIES IN LYMPHOMA

B-cell lymphoma, a type of non-Hodgkin lymphoma, originates in B cells and is characterized by the presence of CD20 on their surface. Bispecific antibodies target CD20 while simultaneously binding CD3 on T cells to recruit them to attack B-cell lymphoma cells. First-line therapy remains systemic chemotherapy, with the intent to cure. However, approximately 40% of patients either relapse or have refractory disease, at which point bispecific antibodies or CAR T-cell therapy become viable treatment options.

The three bispecific antibodies used for B-cell lymphomas are epcoritamab, glofitamab, and mosunetuzumab. While all share structural similarities, glofitamab has a unique 2:1 CD20-to-CD3 binding ratio, distinguishing it from the other two, which have a 1:1 ratio. Each of these therapies employs step-up dosing. Each therapy varies in dosing schedules, response rates, and toxicity profiles, with overall response rates ranging from 56% to 80% across different studies.

"The first dose is to prime the immune system, the second is more of an intermediate dose, and then the third is the full dose and that hopefully decreases the risk of CRS," Ms. O'Brien explained.

Epcoritamab is administered subcutaneously. Hospitalization is recommended for the first full dose, which occurs on cycle 1, day 15. A distinguishing feature is the inclusion of four days of prednisone following the first cycle to mitigate CRS. Patients continue treatment until disease progression or unacceptable toxicity, with complete response (CR) rates observed in approximately 40% of patients.

Glofitamab is given intravenously and follows a similar step-up dosing strategy. Hospitalization is recommended for the first full dose on cycle 1, day 8. Unlike epcoritamab, glofitamab does not require steroid premedication. Instead, patients receive obinutuzumab (an anti-CD20 monoclonal antibody) 7 days prior to treatment to deplete B cells and reduce the risk of CRS. Another key difference is that glofitamab is a time-limited therapy, with a maximum of 12 cycles.

Mosunetuzumab is only indicated for FL. It is administered intravenously and does not have hospitalization requirements. It is given weekly during cycle 1 and every 21 days from cycle 2 onward.

Emerging Trends

In June 2024, a new targeted chemotherapy regimen, VIPOR, was introduced for DLBCL. Additionally, there is increasing interest in the earlier

use of bispecific antibodies and alternative signaling pathways for patients with resistant disease.

MANAGING TOXICITIES

BsAbs are associated with immune-related toxicities such as cytopenias, CRS, and neurotoxicity (immune effector cell-associated neurotoxicity syndrome, or ICANS). Because these reactions can be unfamiliar to patients and caregivers, thorough education is essential to ensure early recognition and intervention.

Cytopenias and Neutropenia

Bispecific antibodies commonly cause neutropenia, defined as an absolute neutrophil count (ANC) of less than 500. To prevent infections, prophylactic strategies should include fluoroquinolone antibiotics (e.g., levofloxacin), antifungal agents (e.g., fluconazole), and antiviral medications (e.g., acyclovir for shingles prevention). Patients receiving corticosteroids may also require *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis. Intravenous immunoglobulin levels should be monitored and replaced if necessary, and delaying treatment or adjusting dosing may be required for prolonged cytopenias.

Cytokine Release Syndrome

Cytokine release syndrome is a systemic inflammatory syndrome triggered by excessive cytokine release from activated T cells. It is more likely in patients with a high tumor burden or preexisting inflammatory conditions and typically occurs during the first cycle of treatment. Data from pivotal clinical trials indicate that CRS occurs in 50% to 70% of bispecific antibody–treated multiple myeloma patients.

Grade 1 CRS involves symptomatic management, with tocilizumab considered if symptoms persist beyond 48 hours. Grade 2 adds dexamethasone 10 mg every 12 hours, while grade 3 increases dexamethasone frequency to every 6 hours alongside tocilizumab administration. In grade 4, dexamethasone is further increased to 20 mg every 6 hours, with continued tocilizumab use and bispecific antibody therapy discontinued.

Although there are recommendations for management and guidance in package inserts, clinical practice can differ.

"I wish I could tell you that our center uses one algorithm to treat CRS, but we have come to recognize that CRS presents a little bit differently in patients who are receiving CAR T-cell therapy vs. patients who are receiving bispecifics," remarked Dr. Mahmoudjafari.

In multiple myeloma, the main recommendation is withholding doses during CRS and resuming treatment only after symptom resolution. If a prolonged dose hold occurs, a step-up dosing regimen may be required upon resumption. With lymphoma there are additional considerations for slowing infusion rates and increasing premedications. In severe cases (grade 4 CRS), permanent discontinuation of therapy is recommended.

ICANS

ICANS symptoms range from mild cognitive impairment to severe neurological dysfunction, including seizures and increased intracranial pressure. ICANS has a median time to onset of about 4 days and generally mild, short-lived symptoms. The ICE (Immune Effector Cell-Associated Encephalopathy) score helps assess neurotoxicity severity, guiding management decisions.

Grade 1 requires withholding the dose until resolution, while grade 2 may involve step-up dosing upon resumption, depending on the duration of the dose hold. Grade 3 may warrant permanent discontinuation of bispecifics, and grade 4 typically necessitates stopping treatment entirely.

Coordination and Education

Outpatient management of grade 1 CRS or ICANS varies by institution, with some centers feeling comfortable if they have the appropriate monitoring tools set in place. However, others may prefer hospital admission. The decision could also be influenced by factors such as timing if it occurs on a weekend, for example. As a result, many institutions admit for observation to make sure patients are stable.

For grade 2 or higher, management typically occurs on the floor with closer monitoring and intervention as needed. "It's important from an education standpoint with our colleagues in the ICU to make sure that they're partners with us and they're cognizant of the adverse events and how we plan on managing them," Dr. Mahmoudjafari

said. It is also important to make algorithms readily available for colleagues.

Another important role for advanced practitioners is to educate caregivers. "Patients and caregivers are used to the chemotherapy-induced nausea, vomiting, diarrhea. These are completely different side effects, so you have to make sure to educate them," said Dr. Mahmoudjafari. "Especially for ICANS—a family member may pick up on it earlier."

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis HLH) is a life-threatening immune hyperactivation syndrome that can occur with bispecific antibody therapy. It presents with a cytokine storm, systemic inflammation, and multi-organ failure. While primary HLH has a genetic cause, secondary HLH, which is more relevant in bispecific antibody-treated patients, is triggered by immune activation. It has a high mortality rate if not treated promptly. Diagnosis is based on Histocyte Society criteria, requiring at least five of the following symptoms: fever, splenomegaly, cytopenias, high triglycerides or low fibrinogen, hemophagocytosis, low NK cell activity, elevated ferritin, and high CD25 levels. Treatment for HLH often requires high-dose corticosteroids, cyclosporine, etoposide, and biologic agents like anakinra to suppress the cytokine-driven inflammation.

GPRC5D-Targeted Bispecific Toxicities

Bispecifics targeting GPRC5D, such as talquetamab, present unique toxicity challenges, particularly mucosal, skin, and nail toxicities. These side effects occur due to GPRC5D expression in keratinized tissues, leading to significant patient discomfort.

Mucosal toxicities include oral pain, ulcers, and dryness, which can be managed with saliva substitutes, sugar-free lozenges, soft foods, and topical treatments. Skin toxicities, which typically appear around day 24 of treatment, are treated with triamcinolone creams, emollients, and systemic corticosteroids if severe. Nail toxicity, a particularly distressing side effect, requires nail strengtheners, moisturizers, and protective care to prevent brittle, painful nails. ●

Disclosure

Dr. Mahmoudjafari has served on advisory boards for Genmab, Janssen, and Sanofi, and as a consultant for Pfizer. Ms. O'Brien has no relevant financial relationships to disclose.

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