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How Do I Optimize Use of Non-Cellular CD19-Targeted Therapies in R/R DLBCL?

Announcer:
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Dr. Caimi:
Hello. My name is Paolo Caimi I'm from Cleveland Clinic, in Cleveland, Ohio. This presentation is on how do I optimize non-cellular based therapies targeting CD19, in relapse, refractory diffuse large B-cell lymphoma.

CD19 has been investigated as a target for immune therapies for several decades. The reason for this interest in CD 19 as a potential target lies on several characteristics. Probably the best known and discussed one is that it is expressed in most stages of B-cell maturation and agents that target CD19 can target and treat a multitude of B-cell disorders. Other less discussed factors are the relative abundance of surface expression amongst CD19 positive cells and the relatively fast internalization and lysosomal processing that happen to antibodies that bind to CD19. These characteristics probably make it an attractive target for both immune therapies that exert their action on the cell surface like monoclonal antibodies, as well as drugs that depend on internalization of the bound receptor, like antibody-drug conjugates.

Two antibody-based drugs target CD19 Tafasitamab, a glycoengineered monoclonal antibody, and Loncastuximab, an antibody-drug conjugate. While both agents are approved for treatment of diffuse large B-cell lymphoma, there were differences in the trials and probably this difference in the population studied, along with the results of the studies, are the most relevant factors when choosing or sequencing these agents. Of course, neither of these drugs can be considered ignoring the existence of CAR T-cells targeting CD19, primarily because of this, cell-based therapies have high activity against diffuse large B-cell lymphoma and may be considered definitive therapies for a subgroup of patients.

The first of these agents is Tafasitamab a glycoengineered monoclonal antibody targeting CD19 with enhancement that increase its affinity for the Fc gamma receptor, which results in higher antibody dependence cytotoxicity and fibrocytosis.

The L-MIND study was a phase 2 trial that included patients with transplant-ineligible, diffuse large B-cell lymphoma who had relapse or refractory disease. Although primary refractive patients were not included. Transplant ineligibility resources included age, organ dysfunction, previous transplant, absence of response to salvage as well, as refusal to go to transplant or failure to collect CD34 cells. The study enrolled 81 patients, and most were of advanced stage, with the median age of 72 years. The median number of lines of therapy was two but 50% had received one line of therapy. 46% were considered ineligible for transplant because of an age of over 70 years.

The primary endpoint of the trial was objective response, with 61% of patients achieving a response and 43% achieving complete response. What has been highlighted is that among the 48 patients presenting disease response, the duration of 21.7 months with 72%,

having a response of more than one year with medium progression free cell variable of 12 months.

The safety assessment of this phase 2 trial suggests a combination of Tafasitamab and . Lenalidomide was relatively well tolerated with hematologic toxicity being the most common and in practice, these patients would frequently need growth factor support and some of the more heavily pre-treated patients will require transfusions. Among nonhematologic toxicities, some were expected with Lenalidomide, such as rash and gastrointestinal symptoms but perhaps relevant to this patient population, the incidence of peripheral neuropathy was low, 1%.

One big logistic hurdle for patients receiving Tafasitamab and Lenalidomide is that this regimen requires significant coordination, including the prescription of Lenalidomide and Tafasitamab as well as a rather intensive schedule with five infusions in the first month, four infusions in the second month and twice every month until progression.

In general my approach to optimizing the treatment of the patient receiving Tafasitamab is, the patient selection is probably the most relevant component. I choose this agent as a second line agent for patients who are both transplant and CAR-T ineligible patient. As most of the patients who are enrolled in the study had had one line of therapy. I generally do not consider this regimen an option for patients with high-risk disease, such as those with primary refractor disease and those with double-hit lymphomas. It is a relatively well tolerated regimen, but this population frequently will need growth factor support. Although I find my patients can be occasionally burdened by the frequent infusions and treatment, until disease progression.

Loncastuximab, our second agent is a CD19 antibody drug conjugate, with a pyrrolobenzodiazepine payload important cytotoxic that causes DNA crosslinking.

The LOTIS-2 trial was a phase two trial that included diffuse large B-cell lymphoma patients that had relapsed or refractory disease to two more lines of therapy. High risk subgroups were included. And those patients presenting progression after CAR T-cell were also eligible, if their disease continued to express CD19. Patients with bulky disease, those with CNS disease and those with recent transplant were excluded. The treatment was given intravenously every three weeks. The first two cycles consisted of a loading dose and then a subsequent decrease in dose and patients were treated for up to 12 months.

Among patients eligible, the median number of previous therapies was three, with inclusion of 10% of double-hit lymphoma. 20% of patients were primary refractory.

The primary endpoint of overall response was 48%, that divided equally among complete and partial responders. Median duration of response was 10.3 months, whereas progression for survival, was five months. Some notable high risk groups included patients with high-grade lymphoma. And those with prior CAR-T cell therapy, With responses that were comparable to those of other groups. In terms of safety, hematologic toxicity again was the most common adverse event. But the remainder of the toxicity profile of Loncastuximab appears to be somewhat different with absence of peripheral neuropathy, but an increase in GDT without hepatic dysfunction and fluid retention events including, edema and plural and pre-cardial infusions. In addition, rash and photosensitivity are important and patients should be instructed to avoid sun exposure.

In my practice, Loncastuximab is an option for patients from different risk groups, including those with double-hit lymphoma and also have had disease progressing after CAR T-cells. I tend to consider Loncastuximab as a treatment alternative for patients with diffuse large B-cell lymphoma who have had CAR T-cells or were CAR T-cell ineligible, Loncastuximab has a safety profile that requires learning and acquiring experience with it. A particular management of the fluid overload and pre-medication can help ameliorate these events. In general, the rate of adverse events and discontinuation is comparable with other agents.

In conclusion, we are fortunate to have a growing number of agents who treat diffuse large B-cell lymphoma that has relapsed after First-line therapy. The drugs targeting CD19 now only a small minority, but a very relevant one. The choice and optimization of these two drugs Loncastuximab and Tafasitamab are based primarily on treating patients with characteristics comparable to those of trials, as well as understanding the expected adverse events and scheduling pitfalls. Thank you for your attention.

Announcer:
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