HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Update on Nivolumab Plus Ipilimumab Combination Therapy for Patients With Hepatocellular Carcinoma

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G&H What is the reasoning behind combining nivolumab and ipilimumab to treat patients with hepatocellular carcinoma?

PG Over the years, we have learned that immune checkpoint inhibitor monotherapy is not as active as we had hoped. This has been demonstrated in several agents, including nivolumab (Opdivo, Bristol Myers Squibb) and pembrolizumab (Keytruda, Merck). These agents interfere with programmed death 1 (PD-1) expression, fostering T-cell response, and are augmented by the addition of other compounds. Atezolizumab (Tecentriq, Genentech) plus bevacizumab combination therapy has shown that additional compounds can result in increased responsiveness, and adding cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors such as ipilimumab (Yervoy, Bristol Myers Squibb) is another option. This has been seen with the Single Tremelimumab Regular Interval Durvalumab (STRIDE) regimen that combines tremelimumab and durvalumab (Imfinzi, AstraZeneca). Nivolumab plus ipilimumab combination therapy also combines 2 checkpoint inhibitors and results in high efficacy, but this combination is different in that the CTLA-4 inhibitor is given 4 times instead of just 1 time in the STRIDE regimen.

This trial showed an objective response rate of 36.1% with nivolumab plus ipilimumab combination therapy, which is the best reported overall response rate that has been seen thus far.

G&H Could you discuss key recent efficacy data on nivolumab plus ipilimumab combination therapy for first-line treatment?

PG The recent CheckMate 9DW trial compared nivolumab plus ipilimumab vs lenvatinib (Lenvima, Eisai) or sorafenib as first-line therapy for patients with unresectable hepatocellular carcinoma (HCC). This trial showed an objective response rate of 36.1% with nivolumab plus ipilimumab combination therapy, which is the best reported overall response rate that has been seen thus far. Not only was response achieved in a high percentage of patients, but it was also very deep and very durable. Thirty-month duration of response was very good, showing the long-term potential of this combination. Overall survival was 23.7 months, which was also very high. At 36 months, 38% of patients receiving nivolumab plus ipilimumab combination therapy were alive compared with 24% in the control arm. Thus, extended lifespan and objective response were seen with nivolumab plus ipilimumab, demonstrating the efficacy of this combination. Based on these data, the US Food and Drug Administration approved nivolumab plus ipilimumab combination therapy for the first-line treatment of adult patients with unresectable or metastatic HCC this past April.

G&H What are the most common adverse events or toxicities with the use of this combination?

PG Skin toxicity (eg, pruritus, rash) is one of the most common adverse events with nivolumab plus ipilimumab combination therapy and is very common in immune oncologic agents overall. Liver-directed toxicity can occur with elevated transaminases, and hypothyroidism and other endocrinopathies can be observed as with other immune oncologic agents. In the CheckMate 9DW trial, there were 12 fatalities in the nivolumab plus ipilimumab arm compared with 3 in the comparator arm, and the discontinuation rate was higher with the combination than in the comparator arm (18% vs 10%, respectively). Thus, there is some toxicity but there is also familiarity with this combination in the medical community, as it has been used for more than 10 years for other indications such as skin tumors. My experience is that this combination can be handled quite well.

> … patients receiving nivolumab plus ipilimumab showed a longer time to liver function deterioration vs controls among all randomized patients, suggesting potential benefit in preserving liver function.

Interestingly, toxicity expectations seem to be quite different when talking to oncologists vs hepatologists. Hepatologists are typically not so experienced in immune oncology combination treatment as oncologists are. Gaining more experience will likely solve some of the negative expectations about toxicity, which, in my opinion, can be handled.

G&H How do these adverse events compare with those of other first-line medical therapies for HCC?

PG In the United States and Europe, essentially 3 combinations are available: atezolizumab and bevacizumab, the STRIDE regimen, and nivolumab plus ipilimumab. Bevacizumab can cause some cardiovascular issues, from bleeding to a stroke and myocardial infarction. Deciding on the combination of CTLA-4 and PD-1 or programmed death ligand 1 inhibitor involves the side-effect profile, which comprises the aforementioned skin and liver toxicity and immune-mediated adverse events. Dosing also matters, as nivolumab plus ipilimumab combination therapy uses 4 doses of ipilimumab compared with 1 dose of tremelimumab in the STRIDE regimen, resulting in more toxicity and then a higher discontinuation rate. It can be argued that, based on this somewhat higher toxicity profile, frailty might be one of the reasons to choose the STRIDE regimen over nivolumab plus ipilimumab. Conversely, a more stable patient might be able to tolerate more toxicity. However, it is necessary to be aware, and this is true not just for toxicity but also for efficacy, that there are no head-to-head comparisons. The patient populations for the 3 combinations were not the same, which might explain the differences in outcome. Therefore, it is presently unclear which treatment to give to which patient, even though the data for nivolumab plus ipilimumab combination therapy are best when looking at long-term outcomes. Toxicity profiles and efficacy expectations should be discussed in multidisciplinary tumor boards to come to a personal decision.

G&H Are there any contraindications or limitations to using nivolumab plus ipilimumab for first-line HCC treatment?

PG Severe and active autoimmune disease requiring treatment (eg, severe, uncontrolled lupus with kidney involvement) can be a contraindication. In clinical reality, it is relatively rare to run into absolute contraindications. There needs to be balance, of course, between toxicity vs efficacy expectations, but, in the end, this is a situation where we have the means to manage side effects. Nearly 30% of patients require high-dose corticosteroids. Although patients benefit from corticosteroids, it is noteworthy that side effects only take a period of, for example, 5 to 6 weeks to begin and then resolution is typically observed by 10 weeks. Thus, this is a limited period where the patient is struggling, and most patients can handle it.

G&H Are there any other recent data on this combination that you would like to highlight?

PG Data presented at this year's meeting of the European Association for the Study of the Liver and later published in *Lancet* have investigated the level of liver function compared with albumin-bilirubin grades. It was interesting to learn that even if patients have poor liver function, the relative efficacy of nivolumab plus ipilimumab is essentially the same with respect to objective response and median

overall survival. However, because liver function is a prognostic factor, patients with poor liver function have a shorter lifespan and nevertheless benefit from therapeutic intervention. In addition, patients receiving nivolumab plus ipilimumab showed a longer time to liver function deterioration vs controls among all randomized patients, suggesting potential benefit in preserving liver function.

G&H How should patients taking nivolumab plus ipilimumab combination therapy be followed?

PG The routine follow-up interval, which is typically different from institution to institution, is in the range of 6 to 12 weeks. Of course, contact should be maintained in order to manage immune-mediated side effects. It is very important that providers are in close contact with patients to step in at an early point and take care of side effects. Laboratory tests, including alpha-fetoprotein, can give an indication as to whether the therapy is effective.

G&H Could you discuss the use of this combination for second- or third-line treatment?

PG In the United States, nivolumab plus ipilimumab combination therapy received accelerated approval from the US Food and Drug Administration in 2020 for second-line HCC treatment based on results from the CheckMate 040 trial. In contrast, nivolumab plus ipilimumab has not been approved in Europe for second- or third-line therapy yet. From what American colleagues report, this regimen is effective, although only small cohorts have demonstrated efficacy in second-line treatment thus far. I think most centers have experience using atezolizumab plus bevacizumab for first-line HCC treatment. Although the CheckMate 9DW trial resulted in approval for first-line treatment in the United States, I know that many colleagues are inclined to use nivolumab plus ipilimumab in the second line of treatment because of its past accelerated approval.

G&H What does the future hold for this combination?

PG Real-world studies are needed because they typically integrate patients who are not part of a clinical trial. Studies concentrate on patients, for example, with good liver function in order to give antitumor therapy a chance to become active. If a patient has poor liver function and/or liver cirrhosis, there might be a strong confounding impact, making it difficult to test the active substance. Even a substance with high antitumor activity will not test positive if liver function is poor and deterioration is taking over. Patients with higher Child-Pugh scores and/or albumin-bilirubin scores, indicating poor liver function, need to be tested in a real-world setting. Data also need to be generated concerning other patients who are typically omitted, such as patients with comorbidities like HIV infection and patients with advanced age.

Finally, it is quite impressive to see the horizontal curves for overall survival after 3 and 4 years of treatment demonstrating that providers can expect even cure in some patients and showing a relevant proportion of complete response. That has resulted in an interesting discussion on conversion therapy. Patients could start with this treatment in a palliative setting, and the result could end up being complete response, leading to discussion on curative treatment options. Conversion therapy as a result of high efficacy is an interesting new aspect of discussion in the field.

Disclosures

Professor Galle has received honoraria from Bayer, Boston Scientific, AstraZeneca, Adaptimmune, BMS, Eisai, MSD, Sirtex, Lilly, Roche, and Guerbet.

Suggested Reading

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