Dear Editor,

It was a great pleasure to read the article, “Feasibility of additional radiotherapy in patients with advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab,” by Kim et al. Combined treatment with radiotherapy (RT) and atezolizumab plus bevacizumab resulted in an objective response rate (ORR) of 71.4% for target lesion within the RT field and of 28.6% for all measurable lesions in seven patients with hepatocellular carcinoma (HCC) of Barcelona Clinic Liver Cancer stage C. The median overall survival (OS) was 14.8 months, and the 1-year local control and OS rates were 60.0% and 87.5%, respectively. There was no severe treatment-related toxicity of grade 3 or higher, except for that in a patient who experienced gastric varix bleeding of grade 3, with the bleeding site located outside the RT field. This study is very meaningful because it deals with the emerging issue of HCC treatment of HCC; however, we have two points on which we would wish to mention.

The first is about the efficacy of the combination of RT and systemic treatment. Manzar et al. reported an ORR of 85% within the RT field and median OS of 6.8 months after the start of RT in patients with HCC treated with atezolizumab plus bevacizumab and RT. Both studies used the same RT techniques of proton beam therapy or intensity-modulated RT and combined treatment regimens. However, there were several differences in the delivery of RT. In the study by Kim et al., 33-66 Gy (median, 35) in 10 fractions was prescribed for tumor thrombus (TT) and/or metastatic lesions after receiving atezolizumab plus bevacizumab. Manzar et al. prescribed 20-75 Gy (median, 60) in 5-25 fractions (80.9% of the patients received a biologically effective dose (BED)) in 10 fractions was prescribed for tumor thrombus (TT) and/or metastatic lesions after receiving atezolizumab plus bevacizumab. Manzar et al. prescribed 20-75 Gy (median, 60) in 5-25 fractions (80.9% of the patients received a biologically effective dose (BED)) in 10 fractions was prescribed for tumor thrombus (TT) and/or metastatic lesions after receiving atezolizumab plus bevacizumab. Increasing the RT dose and expanding the RT field to reduce the tumor burden and increase immune infiltration may enhance the efficacy of immunotherapy. However, the potential risk in the toxicity and the potential for RT to induce cell death in radiosensitive immune cells within the tumor and in local LNs must also be considered. Given that improved RR by RT does not necessarily translate into long-term OS, further research should be needed to define the optimal dose and fraction, RT field, and sequence in combination treatment.
Another important aspect is the safety of the combined use of RT and bevacizumab. In the IMbrave150 trial, grade 3-4 and grade 5 gastrointestinal (GI) bleeding was, respectively, reported in 9% and 2% of patients with HCC treated with atezolizumab plus bevacizumab. All six patients with grade 5 GI bleeding had macrovascular invasion, and four patients had varix or hypertensive gastropathy at baseline. A phase I study of bevacizumab and concurrent capecitabine and RT with 50.4 Gy in 28 fractions followed by maintenance bevacizumab therapy for locally advanced pancreatic cancer showed that among the first 30 patients treated, three had tumor-associated bleeding from duodenal ulcers and one had a contained duodenal perforation adjacent to a tumor within the RT field. No additional bleeding events occurred among the final 18 patients after patients with duodenal involvement by the tumor were excluded. A subsequent phase II study of bevacizumab with concurrent capecitabine and RT followed by maintenance therapy with gemcitabine and bevacizumab defined the RT target as only the gross tumor without elective nodal irradiation. After a retrospective review of RT plans, unacceptable RT protocol deviation (e.g., inappropriately generous volume contoured) were noted in 13.4% of the cases and correlated with GI toxicity ≥ grade 3 (45% vs. 18%; P=0.05). In a phase III study for advanced cervical cancer, bevacizumab was randomly added or not to chemotherapy and fistulas of any grade developed in patients with previous pelvic RT: the rate of grade 3 fistula was 6% in patients who received with bevacizumab vs. <1% in patients who did not receive bevacizumab. Barney et al. reported that seven patients (9%) had GI toxicity ≥ grade 3 after stereotactic body radiotherapy for intra-abdominal lesion. All seven received vascular endothelial growth factor inhibitor therapy: among these, six patients received bevacizumab.

These studies suggest a potential risk of severe GI toxicity due to the combined use of RT and bevacizumab. A simple method to reduce this risk is the discontinuation of bevacizumab, as described by the authors. The half-life of bevacizumab is approximately 21 days. Some researchers suggest waiting at least 6-8 weeks from the discontinuation of RT. However, it is difficult for patients to remain untreated in a real clinical setting. In addition, there is no definitive “wash-out” period. Therefore, efforts are required to minimize the risk of unexpected severe GI toxicity. First, we recommend endoscopy and imaging before RT in patients with HCC treated with bevacizumab. Portal hypertensive gastropathy or direct tumor invasion of the GI mucosa is currently the most relevant risk factor for bevacizumab-related GI toxicity. If these findings are noted, a more conservative approach for prescribing the total RT dose and GI organ constraints should be needed. Second, the simultaneously integrated boost technique, which applies different doses to different targets simultaneously, is considered to reduce the RT dose to GI organs. Third, a more fractionated RT regimen might be helpful in patients with a huge mass, especially those with intra-abdominal metastases, considering that an unexpectedly high incidence of severe GI toxicity occurs when a large volume of GI organs was included within the RT field. Limited clinical data are currently available regarding the combined use of RT and bevacizumab. Therefore, RT should be applied with great caution in bevacizumab-treated patients with HCC until sufficient clinical evidence has been accumulated.

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References


