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EDITORIAL

Can Hypofractionation and Immune Modulation Coexist?

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The past few years have seen a renewed interest in bladder-preserving treatment for patients with muscle-invasive bladder cancer (MIBC). Although there is no doubt that bladder preservation is an excellent local treatment with high levels of control and low levels of late toxicity,[1] about half of patients will die of metastatic disease within 5 years. At the heart of this strategy is radical trimodality treatment (TMT), comprising tumor resection followed by radiation therapy with a radiosensitizer. In current clinical practice, the most commonly used radiosensitizer is chemotherapy, but there is high-level evidence for hypoxia modification with carbogen and nicotinamide as an alternative. Radiosensitization has improved outcomes for patients with MIBC, but a significant impact on overall survival continues to be elusive.

In the age of immunotherapy, could checkpoint inhibitors provide the key? In several preclinical studies, combination therapy with radiation therapy and immune suppressive checkpoint inhibitors such as anti−programmed death-ligand 1 (PD-L1) have been shown to elicit systemic antitumor immune effects.[2] Should this effect translate successfully into the clinic, radiation therapy/anti−PD-L1−based treatment may improve overall survival by eradicating sites of micrometastatic disease before they become clinically evident. Such is the promise of the translational science that there are numerous studies exploring the safety and tolerability of such combination treatment strategies in patients with bladder cancer.

In this issue, Marcq et al[3] report the results of a phase 1 dose-finding study in which they recruited 8 patients with T2-3 N0 M0 MIBC. Patients underwent radiation therapy comprising 50 Gy in 20 fractions to the bladder and prostatic urethra and 40 Gy in 20 fractions to the pelvic lymph nodes, with 100 mg/m^2 of gemcitabine once weekly during radiation therapy. The study protocol included concurrent atezolizumab every 3 weeks and for 16 cycles after completion of radiation therapy. Two of 5 patients treated with 1200 mg atezolizumab developed grade 3 immune-related adverse events (irAEs). Despite receiving a lower dose (840 mg), an additional 2 of 3 patients developed grade 3 irAEs. Gastrointestinal toxicity manifesting as colitis occurred in the majority of these patients, and most discontinued atezolizumab early. There was no grade $\geq$3 urinary-related toxicity. The authors concluded that the regimen of moderately hypofractionated radiation therapy with concurrent gemcitabine and atezolizumab is associated with unacceptable toxicity.

There is no doubt that the rates of grade 3 toxicity reported by Marcq et al are significantly higher than those seen in previous prospective studies investigating the role of conventionally fractionated radiation therapy (RTOG 0712)[4] or hypofractionated treatment with concurrent

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gemcitabine. These trials reported rates of grade 3 gastrointestinal toxicity of less than 10%, even when combined with neoadjuvant chemotherapy.[5] In this case, it is likely that the excessive toxicity observed by Marcq et al is due to the addition of atezolizumab, rather than the chemoradiotherapy regimen itself.

Guidelines advocate different radiation therapy dose and fractionation schedules as part of TMT, and there is a lack of consensus on which should be standard of care. However, a recent meta-analysis using individual patient data from the 2 largest published randomized controlled trials of radiation therapy versus radiosensitization has been performed. This study demonstrated that patients who receive hypofractionated radiation therapy as part of a TMT schedule have better locoregional control than those who undergo conventionally fractionated treatment (adjusted hazard ratio [HR], 0.71; 95% confidence interval, 0.52-0.96) with no increase in toxicity.[6] This effect was observed regardless of radiosensitizer and in patients who received radiation therapy alone. The notion is that moderate hypofractionation mitigates the effect of accelerated repopulation and casts doubt on the assumed high alpha/beta ratio of MIBC. This meta-analysis provides compelling evidence that moderate hypofractionation should be the standard of care for TMT and provides the benchmark for future comparisons.

The study by Marcq et al raises the important question as to whether fractionation may influence toxicity in the context of concurrent treatment with immunotherapy, especially with hypofractionated regimens set to become the standard of care. This concern is initially compounded by outcomes from an earlier phase 1 study examining the role of pembrolizumab (anti−PD-1) in combination with radiation therapy alone to the bladder.[7] Here, patients with locally advanced or metastatic disease were treated with 36 Gy in 6 weekly fractions to the bladder alone. Of the first 5 patients treated, 3 experienced grade 3 urinary toxicity, and 1 developed a rectal perforation. This trial, too, was stopped early. Although both these studies used hypofractionated protocols, the toxicity profiles are very different. Patients who received a much higher dose per fraction in combination with anti−PD-1 treatment, albeit only weekly, developed predominantly urinary toxicity. Those who received moderately hypofractionated treatment (2.5 Gy/fraction) experienced small bowel toxicity, which manifested as colitis, with no significant urinary toxicity. How can we explain this effect? Could it be that the immune response to radiation therapy exhibits fraction sensitivity, which differs between tissues? There are no data published in this area, but the differences between these 2 studies do raise intriguing questions.

Marcq et al used nodal irradiation in their protocol. Nodal irradiation is not standard of care for TMT. Data from the only randomized controlled trial conducted to investigate the value of this suggest that there is no significant benefit.[8] Although organ-at-risk constraints were adequately met, it is likely the mean dose to the bowel in these patients was greater than it would have been if bladder-only treatment had been delivered. A deterministic effect of radiation is to cause release of inflammatory cytokines and infiltration of immune cells in the bowel wall, which can lead to colitis. A previous series reporting toxicity outcomes in patients with MIBC who received the same chemoradiation therapy (including pelvic nodal irradiation) without concurrent immunotherapy demonstrated acceptable toxicity profiles, with rates of grade 3 toxicity of only 4%.[9] The results of Bloggs et al suggest that the addition of anti−PD-1 therapy, which enhances proinflammatory activity, significantly exacerbates this process. If this is the case, then it is the inclusion of pelvic nodes in the irradiated field, rather than the hypofractionated nature of the radiation therapy, which results in the unacceptable toxicity rates seen. This would also explain why colitis was not a significant problem for patients who received 36 Gy in 6 fractions without nodal irradiation in the other study. Furthermore, preclinical evidence has demonstrated that concurrent irradiation of tumor-draining lymph nodes may be detrimental to the generation of synergistic antitumor effects in response to radiation therapy in combination with immune checkpoint inhibition.[10] Removing nodal irradiation from the protocol described by Marcq et al may improve toxicity after combination treatment without compromising the efficacy of the primary chemoradiation therapy.

Antitumor immune effects have been observed in murine models of bladder cancer in response to 1^7 or 2^6 high doses of radiation therapy in combination with anti−PD-1 treatment. However, such extreme hypofractionation may not be required to realize therapeutic synergy, as others have shown similar effects in response to concurrent treatment with a short course of conventionally fractionated radiation therapy (10 Gy in 5 fractions).[10] There is even evidence that single large doses may be detrimental to antitumor immunity in combination with other treatment targeting alternative checkpoints. With no consistent preclinical insights to guide an optimal radiation therapy dose/fractionation to combine with immunotherapy, standard-of-care regimens must be the starting point in the experimental clinical setting.

It is not just the dose and fractionation that must be considered, however. Scheduling of immune checkpoint inhibitors is also important. Preclinical data suggest concurrent anti−PD-1 treatment is required to achieve synergistic antitumor immune effects with radiation therapy. However, a practice-changing study in patients with locally advanced non-small cell lung cancer investigating the addition of adjuvant anti−PD-1 treatment after radical chemoradiation therapy demonstrated a significant improvement in progression-free and overall[11] survival with an acceptable toxicity profile. These patients did not receive immunotherapy concurrently with chemoradiation therapy. Beginning anti−PD-L1 treatment after completion of chemoradiation therapy for MIBC may avoid excessive

toxicity but still lead to improved survival outcomes compared with chemoradiation therapy alone. This hypothesis is being tested in the CCTG BL13 study (NCT03768570).

The SWOG/NRG 1806 trial (NCT03775265), a phase 3 study aiming to investigate the role of atezolizumab administered concurrently and adjuvantly with conventionally fractionated chemoradiation therapy in patients with localized MIBC, opened in 2019. It is recruiting well, having accrued approximately 25% of the intended 475 patients. Patients are stratified according to several parameters. These include the intended chemotherapy regimen (cisplatin vs 5-FU + mitomycin C vs gemcitabine) and radiation field (bladder and pelvic lymph nodes vs bladder alone). So far, there have been no published reports describing excessive toxicity in this study. The endpoints are designed to determine whether the addition of atezolizumab enhances antitumor responses and survival outcomes. However, owing to the prospective incorporation of important stratification factors, SWOG/NRG 1806 should provide robust insights into whether radiation therapy to the pelvic lymph nodes as well as the bladder confers significant toxicity in this setting compared with irradiation of the bladder alone. It may also demonstrate a differential effect of the various chemotherapy agents when combined with atezolizumab. Although this ambitious study seeks to answer a number of important questions, there is no moderate hypofractionation protocol being tested, which in light of the results of the BC2001/BCON meta-analysis will be cause for consideration.

In 2021, even more so as the pandemic continues, we anticipate that use of bladder-preserving TMT, incorporating moderately hypofractionated radiation therapy with concurrent radiosensitization, will become more widespread for many patients with MIBC. Combination treatment strategies with immune checkpoint inhibitors enhancing the antitumor immune stimulatory effects of radiation therapy continue to beguile with the promise of improved survival outcomes for patients with MIBC. Although Marcq et al have demonstrated unacceptable toxicity when anti−PD-L1 treatment was administered concurrently with moderately fractionated chemoradiation to the bladder and pelvic nodes, it is too soon to abandon this area of research. Well-designed studies such as SWOG/NRG 1806 will provide insights into the optimization of combination strategies, especially when the emphasis is on target volume or type of radiosensitizer, but we may need compromise between the known radiobiological benefits of hypofractionation and those promised by concurrent immunotherapy.

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