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Drug–Radiotherapy Combination Trial Developments — Letter

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We read with great interest the comprehensive review by Chargari and colleagues about the challenges of advancing new radiosensitizing drugs through preclinical models and clinical trials.(1) The authors laid out a number of explanations and recommendations for moving forward with more success, and we largely agree with their thoughts. We wish to correct one point used to illustrate the pitfalls of simply adopting chemotherapy agents that have activity when given alone, and the disconnect between preclinical models and eventual clinical results. The authors describe as a cautionary tale the experience with full dose gemcitabine and large-field radiation producing excess toxicity including fatal events. Thus, the authors suggest that gemcitabine dose reduction is the only viable option.

But radiation technique matters too! We wish to draw attention to our long experience at University of Michigan of safely treating borderline and unresectable pancreas cancer with full-dose gemcitabine and radiotherapy. This includes mild hypofractionation (36Gy in 2.4Gy/fx) (2), conventional fractionation (our routine clinical practice) (3), in combination with a novel targeted agent(4), and as part of tri-modality treatment.(5) In our Phase 2 trial, 90% of patients completed gemcitabine-based chemoradiotherapy and there were no deaths. (5) We added a Wee1 inhibitor to gemcitabine-based chemoradiotherapy, and saw G3-4 toxicities that were mostly unrelated to RT (PE, MI, febrile neutropenia, etc). No deaths were due to treatment and all patients completed chemoradiotherapy.(4) Summarizing our experience in 180 patients 1999–2012, 7.7% had late gastric or duodenal bleeding(3), which is similar to what others have found for definitive chemoradiation in this setting.

We treat only gross disease plus a small margin, and do not include elective nodal irradiation. Among the minority of failures that were local, a majority were in-field and not in regional untreated nodal areas indicating that disease control is not compromised.(2) We have been encouraged by our results, with our recent Phase 2 trial after FOLFIRINOX in borderline patients having a 52% resection rate that were all R0 and had a median OS of 37mos.(5) And we continue pursuing the combination of gemcitabine and a Wee1 inhibitor along with radiotherapy after our Phase I/II study in locally advanced patients resulted in a median OS of 22mos.(4)

This experience reinforces the authors' overall message about the search for more effective combinations: safe use of full-dose chemotherapy requires careful consideration both in the crafting of radiotherapy technique as well as the systemic therapy dosing.

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