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LETTER TO THE EDITOR

Commentary on: "Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12"

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Dear Editor:

In recent years, management of locally advanced rectal cancer (LARC) is evolving. We have read with great interest the randomized phase II clinical trial submitted by Fokas and colleagues [1] on the role of total neoadjuvant therapy (TNT) in newly diagnosed LARC patients. The purpose of the CAO/ARO/AIO-12 trial was to determine if a TNT approach had sufficient efficacy for further development in LARC multimodal treatment. It included two arms with different experimental TNT schemes: (i) the neoadjuvant sequence of chemotherapy (CHT) + chemoradiotherapy (CRT) and (ii) the neoadjuvant sequence CRT + CHT. The aim was to expedite the chemotherapy block before surgery—early termination of ineffective approach—and to identify the most effective sequence—pick the winner—to warrant a phase III trial. It was expected that a TNT scheme that could produce a pCR rate of 25% would be likely to produce a clinically meaningful overall survival (OS) and/or progression-free survival (PFS) benefit in the upcoming CAO/ARO/AIO-18 phase III trial.

Briefly, the CRT + CHT positively affected both treatment response and compliance. This TNT sequence significantly improved pathologic complete response (pCR) rate over the common historical control after neoadjuvant CRT (25% versus 15%) and resulted in a less severe CRT-related toxicity profile, despite patients being less likely to complete their consolidation chemotherapy [1]. While these results can provide arguments for treatment selection and guidance, several considerations should be pointed out. First, as discussed by the authors, the trial has pCR as primary endpoint and was designed as part of innovative adaptive method, making the interpretation of trial results difficult. Surely, the randomization strategy was useful to balance unknown confounding factors, reduce selection bias, and create a higher degree of comparability. But the so-called pick-the-winner is usually based on an adaptive randomization design in order to increase the probability of success, but in this trial, each group was designed as a single-arm study, raising an issue of statistical inference [2]. In addition, the improvement of pCR rate is an important goal, but it is essential to verify whether it translates to improved survival outcomes. Second, in the CRT + CHT sequence, the long interval from CRT to surgery (median 90 days, interquartile range (IQR), 85–97) might have contributed to the good pCR results. Whereas, in the up-front CHT sequence, the median interval from CRT end to surgery of 45 days (IQR, 42–53) might have resulted in a failure to reach the predefined statistical hypothesis. This would generate the false impression that the neoadjuvant sequence CHT + CRT is not adequate. But, interestingly, a higher proportion of clinical complete response was recorded in patients treated with the CHT + CRT sequence (6 cases versus 4 cases). These data suggest that postpone surgery might be relevant to achieve higher pCR rate also in this TNT approach. Lastly, the concomitant chemotherapy schedule should be considered. The CRT regimen used—continuous infusion of 5-fluorouracil (5-FU, 250 mg/m^2) on days 1 to 14 and 22 to 35 and a 2-h infusion of oxaliplatin (50 mg/m^2) on days 1, 8, 22, and 29 of radiotherapy—is generally not recommended in the neoadjuvant setting due to potential extra toxicity from oxaliplatin, without a well-defined survival benefit [3]. It could represent a confounder when considering differences in overall clinical outcomes and toxicity profile between the standard preoperative 5-FU-based CRT and the tested TNT sequence in the planned phase III comparison.

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Despite these clarifications regarding trial design and treatment schedule, the results of the CAO/ARO/AIO-12 trial are important to the oncology community. We agree with the researchers that a long follow-up is needed to define the magnitude of TNT efficacy. We deeply believe that improving our knowledge about the comparative effectiveness of TNT strategy and the interval time criteria for surgery would be the major goal.

References

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