Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Radiotherapy and Oncology 151 (2020) 56–57

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

COVID-19 Rapid Letter

Anal cancer treatment regimen considerations for the COVID-19 era: In regard to Tchelebi et al

To The Editor,

We read the article [1] "Recommendations for the use of radiation therapy in managing patients with gastrointestinal malignancies in the era of COVID-19" by Tchelebi et al. with great interest. We commend the authors for providing guidance on various gastrointestinal malignancies during the COVID-19 pandemic. Notably, with regard to the treatment of locally advanced anal cancer, the authors recommend definitive chemoradiation (CRT). The concurrent chemotherapy regimen recommended per the authors is mitomycin-C (MMC) plus capecitabine or fluorouracil (5FU), and that changes to this chemotherapy are not indicated during the global pandemic.

MMC is known to increase the risk of neutropenia and leukopenia, and thus increase the risk of infection. It is critical to be mindful in particular of the hematologic toxicity (HT) of CRT, and therefore, we suggest that there should be careful consideration of the concurrent chemotherapy regimen used in locally advanced anal cancer in the era of COVID-19, a time during which avoiding HT is paramount. RTOG-9811 [2,3], which randomized patients to radiation (RT) + 5FU/MMC versus induction 5-FU/cisplatin (CDDP) followed by RT + 5FU/CDDP demonstrated significantly improved disease free survival (DFS) and overall survival (OS) and a trend towards improved colostomy-free survival (CFS) in the MMC arm. Yet, a crucial caveat of this trial was the use of induction chemotherapy in the CDDP-based arm, which delayed local therapy and potentially leading to more favorable disease-related outcomes in the MMC-based arm. Nevertheless, there was significantly higher grade 3–4 acute HT (62% vs 42%) in patients treated with MMC versus CDDP. The rate of grade 3–4 acute HT was also found to be lower and ranged from 12% to 19% in the CDDP-based regimens of UNICANCER ACCORD-03 [4]. In a 2×2-factorial superiority-design phase III trial, the UKCCR ACT II [5] study randomized patients to MMC-based CRT versus CDDP-based CRT followed by CDDP-based maintenance chemotherapy versus no maintenance. In ACT II, the largest anal cancer trial to date, disease-related outcomes of DFS, OS, and CFS were not significantly different between the CDDP and MMC-based arms. Yet, acute HT (grade 3–4, 26% vs 16%) was higher in the MMC arm. Despite CDDP-based regimens having comparable outcomes as shown in ACT II with less acute HT, MMC-based regimens continue to be more commonly used in locally advanced anal cancer.

Even in the pre-COVID-19 era, our institutional practice has always favored using the doublet of CDDP/5FU weekly in an effort to reduce acute HT in all patients with anal cancer, but particularly among immunocompromised (such as those with human immunodeficiency virus [HIV] infection) and older patients, both of whom are prone to anal cancer. Notably, earlier anal cancer trials excluded those with HIV infection, who are not only at increased risk for anal cancer but are also more susceptible to HT from CRT. At our institution, we administer CDDP (20 mg/m^2 weekly) with 5FU (300 mg/m^2/day on days of radiation). In our published experience [6] of 197 patients with locally advanced anal cancer treated with concurrent CDDP/5FU and RT, there was only one patient that developed grade 3 neutropenia. Moreover, grade 4 myelosuppression was not observed. Weekly administration of CDDP/5FU in our retrospective analysis resulted in a more favorable HT profile for this patient population than prior prospective experiences with CDDP/5FU (such as ACT II), which were administered on weeks 1 and 5. This CDDP-based regimen was not only well-tolerated, but was also just as clinically effective (5-year DFS 81%, 5-year OS 86%, and 5-year CFS 88%).

Together, we submit that the doublet of CDDP/5FU should be strongly considered as part of concurrent CRT in the treatment of locally advanced anal cancer during the pandemic, when avoiding HT in patients who are already at risk for severe infection from COVID-19 is of utmost importance.

Funding

No funding.

Authorship

All authors contributed equally to this reply.

Disclosures

Sonal S. Noticewala MD, MAS (none); Ethan B. Ludmir, MD (none); Cathy Eng, MD (none); Emma B. Holliday, MD (unrelated Merck-sponsored research projects), Bruce D. Minsky, MD (none), Van K. Morris, MD (none), Prajnan Das, MD, MS, MPH (related honoraria and Vice Chair role at National Cancer Institute Rectal-Anal Task Force/Leidos; unrelated honoraria from Adlai Nortye, MD Anderson Cancer Center Madrid, and American Society for Radiation Oncology).

References

[1] Tchelebi LT, Haustermans K, Scorsetti M, et al. Recommendations for the use of radiation therapy in managing patients with gastrointestinal malignancies in the era of COVID-19. Radiother Oncol 2020;148:194–200. https://doi.org/10.1016/j.radonc.2020.04.010.

[2] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized controlled trial. JAMA - J Am Med Assoc 2008. https://doi.org/10.1001/jama.299.16.1914.

[3] Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI intergroup RTOG 98–11 Phase III trial for anal carcinoma: Survival, relapse, and colostomy

https://doi.org/10.1016/j.radonc.2020.07.028

failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012. https://doi.org/10.1200/JCO.2012.43.8085.
[4] Peiffert D, Tournier-Rangeard L, Gérard JP, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol 2012. https://doi.org/10.1200/JCO.2011.35.4837.
[5] James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial. Lancet Oncol 2013;14(6):516–24. https://doi.org/10.1016/S1470-2045(13)70086-X.
[6] Eng C, Chang GJ, You YN, et al. Long-term results of weekly/daily cisplatin-based chemoradiation for locally advanced squamous cell carcinoma of the anal canal. Cancer 2013. https://doi.org/10.1002/cncr.28296.

Sonal S. Noticewala [a]
Ethan B. Ludmir [a]
Cathy Eng [b]
Emma B. Holliday [a]
Bruce D. Minsky [a]
Van K. Morris [c]
Prajnan Das [a,*]
[a] *Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, United States*
[b] *Department of Gastrointestinal Oncology, Vanderbilt-Ingram Cancer Center, Nashville, United States*
[c] *Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, United States*
* Corresponding author at: The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit Number: 1422, Houston, TX 77030, United States.
E-mail address: prajdas@mdanderson.org (P. Das)
Received 6 July 2020
Accepted 14 July 2020

Available online 22 July 2020