Editorial Commentary

DNA-dependent protein kinase inhibitor as a sensitizer of radiotherapy in locally advanced rectal cancer

Yoshinori Kagawa[1,2]^, Jun Watanabe[3]^, Koji Ando[4]^

[1]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan; [2]Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Japan; [3]Department of Colorectal Surgery, Kansai Medical University, Osaka, Japan; [4]Department of Surgery and Science, Kyushu University, Fukuoka, Japan

Correspondence to: Yoshinori Kagawa, MD, PhD. Department of Gastroenterological Surgery, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka 541-8567, Japan; Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Japan. Email: yoshinori.kagawa@oici.jp.

Comment on: Romesser PB, Capdevila J, Garcia-Carbonero R, *et al*. A Phase Ib Study of the DNA-PK Inhibitor Peposertib Combined with Neoadjuvant Chemoradiation in Patients with Locally Advanced Rectal Cancer. Clin Cancer Res 2024;30:695-702.

Keywords: Locally advanced rectal cancer (LARC); DNA damage repair (DDR); DNA-dependent protein kinase inhibitor (DNA-PK inhibitor)

Submitted May 19, 2024. Accepted for publication Aug 29, 2024. Published online Oct 09, 2024.
doi: 10.21037/jgo-24-373
View this article at: https://dx.doi.org/10.21037/jgo-24-373

Generally, locally advanced rectal cancer (LARC) is treated by neoadjuvant chemoradiotherapy (nCRT) or total neoadjuvant therapy (TNT) to improve both short- and long-term outcomes (1). Patients who achieve a pathologic complete response (pCR) with TNT may choose to adopt a nonoperative management strategy (NOM), which avoids surgery and preserves quality of life (QOL) without sacrificing their long-term prognosis. Nevertheless, the rates of pCR and complete clinical response (cCR) remain suboptimal, limiting the number of patients who are eligible for NOM (2). The enhancement of pCR and cCR rates through preoperative treatments is a critical unmet need, with the objective of expanding the number of candidates for this approach. In this context, the development of combination radiotherapy with immunological agents or molecular targeted therapies is also underway, with the objective of enhancing the efficacy of radiotherapy. Phase Ib results of peposertib, a DNA-dependent protein kinase (DNA-PK) inhibitor, as a sensitizer for chemoradiotherapy (CRT) for LARC were published in the *Clinical Cancer Research* journal in 2024 (3).

Peposertib has been preclinically demonstrated to inhibit the catalytic activity of DNA-PK with high potency and the double-strand breaks (DSB) repair in human cancer cell lines (4). Furthermore, peposertib inhibits radiation-induced DNA-PK autophosphorylation and DSB repair in tumor xenograft models. Oral administration of peposertib to two xenograft models of human cancer, utilizing a clinically established 6-week fractionated radiation protocol, markedly enhanced the tumor growth inhibition of radiotherapy, leading to complete tumor regression at nontoxic doses. Therefore, peposertib was a strong candidate for combination with radiotherapy based on preclinical data.

Romesser *et al.* (3) conducted a phase Ib study to assess the efficacy and safety of combining peposertib with capecitabine-based CRT in patients with LARC. A dose escalation was conducted to determine the maximum tolerated and recommended phase II dose of peposertib. The results demonstrated that doses up to 150 mg administered once daily were tolerable; however, dose-limiting toxicities were observed at higher doses. Although 15.8% of patients achieved cCR, pCR had only 5.3% upon surgery. The efficacy of the combination with peposertib and capecitabine-based CRT did not demonstrate a clear clinical benefit for patients with LARC (3).

^ ORCID: Yoshinori Kagawa, 0000-0001-6876-4507; Jun Watanabe, 0000-0002-7187-3664; Koji Ando, 0000-0002-0149-1505.

There is growing interest in the development of drugs that target DNA damage repair (DDR) to enhance radiotherapy efficacy (5). Given the critical role of DDR in maintaining DNA integrity, drugs that target this process have been developed, owing to the concept of "synthetic lethality," which posits that when one or more DDR pathways cease to function, cells become more dependent on the remaining DDR pathways for survival (6). Similarly, if mutations in a cancer cell result in the loss of a major DDR pathway, such a cell will rely on a backup pathway for survival.

DNA-PK, one of the DDRs, is also a new target. Among DNA damage categories, DSBs are the most deleterious and are crucial for the efficacy of cancer therapy with radiation, topoisomerase II inhibitors, and other agents. DSBs are primarily repaired by two distinct mechanisms: non-homologous end joining (NHEJ) and homologous recombination (HR). Both mechanisms are essential in maintaining chromosomal stability. Mediated by the ataxia telangiectasia-mutated (ATM) protein, HR is responsible for repairing DSBs with minimal errors. However, this process is mainly active during the S-phase of the cell cycle. Meanwhile, NHEJ can function at any phase of the cell cycle and is the major DSB repair system in higher eukaryotes. This process is more error-prone than HR, though rapid and efficient. DNA-PK, which plays a pivotal role in NHEJ, consists of a catalytic subunit and the proteins Ku70 and Ku80. These proteins are critical for DSB repair via NHEJ throughout the cell cycle. In line with this, cells lacking DNA-PK are sensitive to DSB-inducing agents, and DNA-PK inhibitors can reproduce this effect. Similar to ATM, DNA-PK inhibitors combined with radiotherapy have emerged as an appealing anticancer strategy. Consequently, DNA-PK is regarded as a promising target for radiosensitization, and numerous DNA-PK inhibitors have been developed. Many of these inhibitors have proven invaluable for investigating DNA-PK functions in basic research. However, the specificity of these inhibitors is insufficient for clinical use. Currently, DNA-PK inhibitors such as peposertib, AZD7648, and CC-115 have been evaluated in clinical trials in combination with radiation therapy (5).

The first clinical trial utilizing peposertib was conducted in 2014 (7). In the initial investigation involving humans, peposertib was well tolerated in patients with advanced solid tumors. Currently, numerous ongoing trials are investigating the potential benefits of peposertib combined with chemotherapy, radiotherapy, or immunotherapies in small-cell lung cancer, acute myeloid leukemia, prostate cancer, hepatobiliary malignancies, ovarian cancer, pancreatic cancer, glioblastoma or gliosarcoma, head and neck cancer, neuroendocrine tumors, and rectal cancer (*Table 1*) (5). Recently, a phase 1 study of peposertib combined with radiotherapy with or without cisplatin has demonstrated that this combination was well tolerated up to doses of 200 mg once daily (tablet) with each radiotherapy fraction in patients with advanced head and neck tumors (9). However, a phase 1 study of peposertib and avelumab with or without palliative radiotherapy in patients with advanced solid tumors exhibited tolerability but no clinical benefit (8).

The development of drugs that selectively inhibit the backup pathway may potentially induce cell death in cancers with specific mutations. Furthermore, drugs that target DDR could be combined with radiotherapy or chemotherapy to enhance the treatment of specific cancers. For LARC, the combination of veliparib, a poly (ADP-ribose) polymerase inhibitor (PARPi), with capecitabine and radiotherapy was found to be safe and exhibited a dose-proportional pharmacokinetic profile (10). Although a 29% pCR rate was achieved, the preliminary antitumor activity requires further evaluation. In the long-term result of NRG-GI002, the addition of veliparib to TNT showed no significant differences in tumor response or 3-year outcomes (11).

To enhance local responses and long-term outcomes following TNT, it is essential to innovate radiation sensitizers and develop treatment regimens (1,12). It has been demonstrated that radiotherapy and chemotherapy induce genomic and chromosomal instability. The DDR plays a pivotal role in this process. Consequently, DDR inhibitors act as sensitizers in cancer cells, enhancing the efficacy of radiotherapy and chemotherapy (13). Additionally, genomic and chromosomal instability can serve as a trigger for the activation of innate immune pathways and adaptive immunity, thereby initiating antitumor responses. The concurrent administration of chemotherapy, radiotherapy, and DDR inhibitors has been demonstrated to enhance the eradication of tumors by stimulating the activation of interferon (IFN)-dependent T cells. (12). It is therefore possible that a new treatment option for patients with locally advanced and metastatic tumors may be combination therapy based on the theory that DNA damage-inducing therapy and immune checkpoint inhibitors (ICIs) with a synergistic effect on tumor regression.

The findings of the trial for DDR inhibitors and

Table 1 Selected clinical trials for peposertib

Cancer types	Phase	Combination	Clinical trial ID[†]
Rectal cancer	Ib	Radiotherapy, capecitabine	NCT03770689 (3)
Advanced solid tumors	I	Radiotherapy, cisplatin	NCT02516813
		Radiotherapy, avelumab	NCT03724890 (8)
		M1774	NCT05687136
Glioblastoma	I	Radiotherapy, temozolomide	NCT04555577
Renal cell carcinoma	I	177Lu-TLX250	NCT05868174
Small cell lung cancer	I	Cisplatin, etoposide	NCT03116971
Advanced solid tumors, chronic lymphocytic leukemia	I	–	NCT02316197 (7)
Advanced/metastatic solid tumors, cholangiocarcinoma, gallbladder carcinoma	I/II	Radiotherapy, avelumab	NCT04068194
Neuroendocrine tumors	I	Lutetium Lu 177 dotatate	NCT04750954
Endometrioid adenocarcinoma	I	Pegylated liposomal doxorubicin hydrochloride	NCT04092270
Head and neck squamous cell carcinoma	I	Radiotherapy	NCT04533750
		Radiotherapy ± cisplatin	NCT02516813 (9)
Leiomyosarcoma, sarcoma	I	Pegylated liposomal doxorubicin hydrochloride	NCT05711615
Prostate carcinoma	I/II	Radium-223 dichloride ± avelumab	NCT04071236

[†], clinical trials are accessible at https://clinicaltrials.gov/.

radiotherapy (3,11) for patients with LARC are intriguing, encouraging investigators to conduct a more thorough data analysis to identify the underlying biomarkers for the complete response. Indeed, the combination of DDR inhibitors with radiotherapy may be optimized by a comprehensive molecular analysis including whole exon sequencing (WES) and whole transcriptome sequencing (WTS) of circulating tumor DNA/RNA, spatial transcriptome sequencing, WES/WTS of tissue samples, plasma proteomic profiling and germline analysis, conducted via supercomputing system (14).

The latest edition of the guidelines adopts a biomarker-driven approach with regard to patients with LARC (15). ICI monotherapy in LARC patients with deficient mismatch repair (dMMR) leads to clinical complete response, organ preservation and sustained QOL (16). Moreover, the OPRA trial demonstrated the approximately 50% potential of NOM following TNT for patients with proficient MMR (pMMR) as an option to reduce morbidity without sacrificing disease control in LARC (2). Accordingly, a more precise ability to predict eventualities for the purposes of guiding treatment strategies at diagnosis and/or restaging would be beneficial. To facilitate the precision oncology in LARC, international collaborations (1) have been already established to integrate multi-omics data from ongoing TNT clinical trials. These include the JANUS Rectal Cancer Trial (A022104/NRG-GI010/NCT05610163), the ACO/ARO/AIO18.1 trial (NCT04246684), and the ENSEMBLE trial (NCT05646511) (17-19). This collaboration will encompass multi-omics data, including genomics, transcriptomics, proteomics, pathomics, radiomics, clinical features, and QOL data. The deployment of an artificial intelligence-based model for precise targeted treatment of LARC through a supercomputing system will facilitate the delivery of precision medicine to individual patients (1,14). A comprehensive spatio-temporal multi-omics analysis employing supercomputers will bring about an era wherein individual patients will receive an appropriate treatment strategy utilizing chemotherapy, radiotherapy, ICIs, DDR inhibitors, and other methodologies.

With the progress of "precision oncology", for patients with dMMR rectal cancer, ICIs have opened the door to a cure. For patients with pMMR rectal cancer, a keyhole to cure without surgery is being opened through a multidisciplinary approach that includes DNA-PK inhibitors as radiotherapy sensitizers.

Acknowledgments

We are grateful for the support of Yoshimi Shinomiya from the Osaka General Medical Center.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article has undergone external peer review.

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-373/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-373/coif). Y.K. discloses payment or honoraria from Lilly, Sanofi, Takeda, Merck, Taiho, MSD, Chugai, Bayer, and Ono. J.W. reports receiving honoraria for lectures from Johnson and Johnson, Medtronic, Eli Lilly and Takeda Pharmaceuticals, and receiving research funding from Medtronic, TERUMO and Stryker Japan outside the submitted work. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kagawa Y, Watanabe J, Ando K. DNA-dependent protein kinase inhibitor as a sensitizer of radiotherapy in locally advanced rectal cancer. J Gastrointest Oncol 2024;15(5):2358-2362. doi: 10.21037/jgo-24-373