Editorial Commentary

*UGT1A1**6 genotype in Asian population and hard endpoint for locally advanced rectal cancer

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Zhu *et al.* (1) have reported a phase 3 trial comparing capecitabine neoadjuvant chemoradiotherapy with capecitabine plus irinotecan neoadjuvant chemoradiotherapy (XELIRIRT) for the treatment of locally advanced rectal cancer. Their results showed that the addition of irinotecan improved the pathological complete response (pCR) rate from 15% to 30% [risk ratio =1.96; 95% confidence interval (CI) 1.30 to 2.97; P=0.001]. Despite these encouraging results, some aspects of this trial warrant closer attention.

First, as the authors pointed out in their Discussion, the *UGT1A1**6 allele was not considered in this study. In Asian populations, the frequency of *UGT1A1**6 is known to be particularly high. The AXEPT study reported that the *UGT1A1**6 genotype, including *UGT1A1**6 single heterozygote and *UGT1A1**6*28 double heterozygotes, was present in 22% of the subjects (2). If this population had been excluded, the XELIRIRT regimen would have been more tolerable.

Second, a cycle of capecitabine plus irinotecan (XELIRI) was administered after completion of XELIRIRT. In this study, XELIRI consisted of capecitabine (1,000 mg/m^2) administered twice daily on days 1–14 and irinotecan (200 mg/m^2) administered on day 1. XELIRI consisting of capecitabine (1,000 mg/m^2) and irinotecan (250 mg/m^2) was too toxic and was not tolerated in the BICC-C and CAIRO studies (3,4). Modified XELIRI regimens consisting of capecitabine (1,000 or 800 mg/m^2) and irinotecan (200 mg/m^2) were examined in the ACCORD13 and AIO0604 studies, respectively (5,6). These regimens were particularly well tolerated in terms of diarrhea.

Third, although grade 3–4 neutropenia and diarrhea during XELIRI were not shown in this study, grade 3–4 neutropenia (47.8%, 26%, 12%, and 16%) and diarrhea (31.9%, 7%, 18%, 10%) were seen in the BICC-C, CAIRO, ACCORD13, and AIO0604 studies, respectively (3-6). In the AXEPT study, XELIRI with or without bevacizumab (which was regimen used in the AIO0604) was associated with grade 3–4 neutropenia (16.8%) and diarrhea (7.1%) in an Asian population (7,8). It is limited to one cycle of XELIRI consisting of ACCORD13 regimen after the completion of XELIRIRT in this study and tolerability may not have been a concern, but XELIRI consisting of AIO0604 regimen may also be considered depending on toxicity.

Fourth, although capecitabine plus oxaliplatin (XELOX) has been established as a gold standard adjuvant chemotherapy, was postoperative XELIRI an option at the time of study planning? If tumor regression was observed during XELIRIRT, postoperative XELIRI could have emerged as an option. A switch in treatment, XELIRI followed by XELOX, could be used as a reasonable treatment strategy considering susceptibility of tumors to chemotherapeutic agents. On the other hand, the biology of tumors refractory to this treatment strategy may be extremely poor.

Finally, the primary end point of this study was the pCR. Cancer treatment also aims to extend survival or improve quality of life. In this regard, overall survival (OS) has been a hard end point and has traditionally been the main outcome in clinical trials. However, more recent trials have used

disease-free survival or progression-free survival as end points to shorten study time. The OS data from this study have not yet been mature; an analysis after a median follow-up of 3 years is designed to determine conclusively the OS benefit of XELIRIRT followed by surgery and adjuvant XELOX for locally advanced rectal cancer. It is important to understand which drugs and radiotherapy benefit from OS when used in an adjuvant setting without compromising long-term survival. OS is a critically important end point for clinicians to consider when choosing chemoradiotherapy for locally advanced rectal cancer and will undoubtedly become more prominent as our treatment options expand.

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