Are Mutations of the EGFR Gene Promising Predictive Markers for Anti-EGFR mAbs in Colorectal Carcinomas?

Dong-Guk Park

Department of Surgery, Dankook University School of Medicine, Cheonan, Korea

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Expression of epidermal growth factor receptor (EGFR) was found in 60-75% of colorectal carcinomas. Based on this, many studies have demonstrated the efficiency of monoclonal Abs (mAbs) in targeting the EGFR, such as cetuximab and panitumumab, in metastatic colorectal cancer (mCRC) patients. Addition of cetuximab to irinotecan-based chemotherapy significantly improved the response rate and the progression-free survival (PFS) when compared with Cetuximab mAb alone (22.9% vs. 10.8% and 4.1 vs. 1.5 months, respectively) [1].

Van Cutsem et al. [2, 3] reported that in chemo-naïve mCRC patients, the addition of anti-EGFR to irinotecan-based chemotherapy led to an 8.2% increase in the objective response (46.8% vs. 38.4%), a 0.9-month increase in the progression free survival (PFS) (8.9 vs. 8 months) and a 1.3-month increase in the overall survival (19.9 vs. 18.6 months). Initially, the use of anti-EGFR mAbs was restricted to mCRC patients with expression of EGFR that was detectable using immunohistochemistry. However, due to the lack of immunohistochemistry predictive value and the variable clinical response, more reliable predictive markers of the response to anti-EGFR mAbs are needed [4].

Two types of molecular predictive markers have been investigated. The first is somatic mutations in EGFR pathway effectors, such as RAS-RAF-MAPK and PI3K-Akt-PTEN. Amplification of EGFR and overexpression of EGFR ligands are associated with sensitivity to anti-EGFR mAbs, but the mutations of BRAF and PIK3A and the loss of PTEN expression are associated with resistance to anti-EGFR mAbs [2, 5]. The second is germline polymorphisms of genes involved in the EGFR path-

way [6]. Nonetheless, at the present time, mutation of KRAS is the only negative molecular marker to anti-EGFR mAbs treatment [2, 5]. Recently, a somatic mutation of the EGFR kinase domain was initially reported in lung cancer and later in colorectal carcinomas. In lung cancer, mutations in the EGFR gene are associated with a high response rate to EGFR tyrosine kinase inhibitors and are prognostic for a favorable outcome.

In this paper, the authors reported the incidence of the EGFR mutation in colorectal carcinomas as 22.41%. The incidence was higher than reports in Western countries, and the EGFR mutation was increased in earlier stages and in the absence of lymph node metastasis. Also exon 20 was the only mutation site, which is different from reports in Japan (mutations in exon 19 and 20). The EGFR mutation state may be an important determinant in the resistance to anti-EGFR mAbs treatment. To address this, larger studies are needed, and hopefully it will be another predictive marker for anti-EGFR mAbs therapy in mCRC [7].

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Correspondence to: Dong-Guk Park, M.D.

Department of Surgery, Dankook University School of Medicine, San 16-5 Anseo-dong, Dongnam-gu, Cheonan 330-715, Korea
Tel: +82-41-550-3931, Fax: +82-41-565-6167
E-mail: dgpark@dankook.ac.kr

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