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When to screen and not to screen

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Commentary to: Esposito C, Rachiglio AM, La Porta ML, Sacco A, Roma C, Iannaccone A, Tatangelo F, Forgione L, Pasquale R, Barbaro A, et al. The S492R EGFR ectodomain mutation is never detected in KRAS wild type colorectal carcinoma before exposure to EGFR monoclonal antibodies. Cancer Biol Ther 2013; 14:1143-6; PMID:24025416; http://dx.doi.org/10.4161/cbt.26340

Colorectal cancer (CRC) is the third most common cause of cancer-related deaths with treatment of advanced and metastatic CRC (mCRC) remaining palliative at best.[1] The epidermal growth factor receptor (EGFR) has been identified as a therapeutic target for a multitude of malignancies, including mCRC. Ligand-binding to EGFR results in the subsequent activation of multiple signal transduction pathways including the PI3K/AKT and RAS/RAF/MAPK pathways, which are vital for cell growth and survival.[2] Constitutive activation of these signaling pathways leads to deregulated cellular proliferation, malignant progression, and invasion.[3]

At present, the EGFR monoclonal antibodies (mAbs) cetuximab and panitumumab have been approved for the treatment of mCRC and have resulted in modest stabilization of disease; however, resistance to mAbs has been reported when administered as monotherapy.[4,5]

KRAS (Kirsten rat sarcoma-2 virus oncogene), a signal transducer, acts in response to stimulation of EGFR and is mutated in approximately 35–45% of CRCs.[1] KRAS mutations are strongly associated with resistance of CRC tumors to EGFR mAbs therefore only KRAS wild-type patients are considered for this form of therapy.[6,7] The mechanism of resistance to EGFR mAbs have been attributed to overexpression of ErbB2 or further mutations within the EGFR receptor, such as S492R. The acquisition of EGFR mutation S492R occurs after exposure to cetuximab in mCRC and conveys resistance to cetuximab but not to panitumumab. In addition, activation of downstream signaling pathways of EGFR, such as mutations in KRAS or BRAF, have also been associated with progression of CRC and subsequent resistance to EGFR mAbs.

The current study investigates the incidence of S492R EGFR mutation in KRAS wild-type CRCs prior to subjection to EGFR mAbs.[8] Five hundred and five therapy-naïve CRC formalin-fixed paraffin-embedded tissues were examined for the S492R mutation to ascertain whether patients should be routinely screened for this mutation prior to treatment. The S492R mutation was not detected in any of the samples analyzed in this study; consequently the authors concluded that the S492R mutation is unlikely involved in primary resistance and thus screening prior to treatment is not required.

Inconsistencies exist in the analysis of the paraffin-embedded tissue samples. Although all were KRAS-exon 2 wild type and therapy-naïve, the samples were heterogeneous in malignant staging and origin, 93% of the samples were derived from primary tumors whereas the remaining 7% obtained from nodes.[8] In addition, while the mutation detection assay developed had a threshold of 10% mutant DNA detection in a background of wild-type DNA, a more sensitive technique is required to ensure detection of low levels of mutated alleles. The authors' concern that increased sensitivity of detection may result in exclusion of therapy sensitive patients is a valid point.

Previous results suggest that KRAS mutations and overexpression of ErbB2 are involved in both intrinsic and acquired resistance to EGFR mAbs. In contrast, the S492R mutation is not detected prior to exposure to cetuximab and is therefore exclusively a mechanism of acquired resistance.[8] In addition, the authors state that

there may be a possible overlap between acquired and intrinsic resistance that requires thorough evaluation. This study is useful as it indicates that the S492R mutation is not involved in primary resistance to cetuximab in CRC, implying that patients with mCRC do not need to be routinely screened for this mutation prior to therapy with EGFR mAbs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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