CORRESPONDENCE

The Treatment of Colorectal Carcinoma With Monoclonal Antibodies—The Importance of KRAS Mutation Analysis and EGFR Status

by Dr. med. Sebastian Stintzing, Prof. Dr. med. Volker Heinemann, PD Dr. med. Andreas Jung, Dr. med. Nicolas Moosmann, Prof. Dr. med. Wolfgang Hiddemann, Prof. Dr. med. Thomas Kirchner in volume 12/2009

Subsequent Immunological Mechanisms

The effectiveness of monoclonal antibodies in oncology and hematology depends—in addition to their effect on the "target"—on whether subsequent immunological mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) are triggered. It is regarded as confirmed that ADCC and CDC depend on sufficient glycosylation of the antibodies. The extent of ADCC is determined by the FcγRIII (CD64) polymorphism and the FcγRIII (CD16a) polymorphism of the Fc moiety of the IgG1 isotype of the monoclonal antibodies. This mechanism has been shown for rituximab in the treatment of follicular lymphoma (1), for trastuzumab in metastatic breast cancer (2), and for cetuximab in the treatment of metastatic colorectal cancer (3). Panitumumab as a human monoclonal antibody of the IgG2 isotype does not trigger ADCC but may trigger CDC and, if administered sequentially, the formation of anti-idiotypic antibodies. The two other EGFR directed antibodies that need mentioning are matuzumab and nimotuzumab. Nimotuzumab is of particular interest because in the treatment of pediatric malignant gliomas and in non-small cell bronchial carcinoma it did not show any symptoms of the known cutaneous toxicity, especially not acneiform exanthema. This antibody has been licensed in several European countries and is currently being tested in phase III trials for further indications.

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REFERENCES

1. Weng WK, Levy R: Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol* 2003; 21: 3940–7.
2. Musolino A et al.: Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. *J Clin Oncol* 2008; 26: 1789–96.
3. Bibeau F et al.: Impact of Fc[gamma]RIIIa-Fc[gamma]RIIIa polymorphisms and KRAS mutations on the clinical outcome of patients with metastatic colorectal cancer treated with cetuximab plus irinotecan. *J Clin Oncol* 2009; 27: 1122–9.
4. Stintzing S, Heinemann V, Jung A, Moosmann N, Hiddemann W, Kirchner T: The treatment of colorectal carcinoma with monoclonal antibodies—the importance of KRAS mutation analysis and EGFR status. *Dtsch Arztebl Int* 2009; 106: 202–6.

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In Reply:

As Tsamaloukas rightly comments, antibody mediated cellular cytotoxicity may be a further mechanism of action of the anti-EGFR antibody cetuximab. The studies reported by Zhang (1) and Bibeau (2) are the first retrospective studies that have shown a clinical effect of the FcγRIIIA(CD64) polymorphism and the FcγRIIIa (CD16a) polymorphism of the Fc-receptor on macrophages and/or natural killer cells on ADCC.

It needs to be emphasized, however, that larger studies (3) have not shown a clear indication of the efficacy of cetuximab on KRAS mutated tumors as described by Bibeau. In these studies, which were also retrospective investigations, the use of cetuximab in KRAS mutated patients with colorectal cancers did not result in a significantly prolonged progression-free survival. In one study, patients who were treated with FOLFOX and cetuximab and had a KRAS mutation responded less well and had a shorter progression-free survival interval (3) than patients treated with FOLFOX. Prospective studies with larger numbers of patients are thus needed to better assess the concrete effect of ADCC.

Because of the currently unclear importance of ADCC, anti-EGFR antibodies should not be used in patients who have KRAS mutations.

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REFERENCES

1. Zhang W et al.: FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. *J Clin Oncol* 2007; 25: 3712–8.
2. Bibeau F et al.: Impact of Fc[gamma]RIIIa-Fc[gamma]RIIIa polymorphisms and KRAS mutations on the clinical outcome of patients with metastatic colorectal cancer treated with cetuximab plus irinotecan. *J Clin Oncol* 2009; 27: 1122–9.
3. Bokemeyer C et al.: Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; 27(5): 663–71.
4. Stintzing S, Heinemann V, Jung A, Moosmann N, Hiddemann W, Kirchner T: The treatment of colorectal carcinoma with monoclonal antibodies—the importance of KRAS mutation analysis and EGFR status. *Dtsch Arztebl Int* 2009; 106: 202–6.

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Conflict of interest statement

The authors of both the letter and of the reply declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.