Monoclonal Antibodies in the Treatment of Metastatic Colorectal Cancer: A Review

Jolien Tol, MD; and Cornelis J.A. Punt, MD, PhD

Department of Medical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

ABSTRACT

Background: Two groups of agents targeting either the vascular endothelial growth factor (VEGF) receptor or the epidermal growth factor receptor (EGFR) have been added to the therapeutic arsenal against metastatic colorectal cancer (mCRC). Currently available agents in these groups are the anti-VEGF antibody bevacizumab and the anti-EGFR antibodies cetuximab and panitumumab.

Objectives: This article reviews the results of prospective randomized clinical trials of anti-VEGF and anti-EGFR antibodies in mCRC, either as monotherapy, combined with chemotherapy, or combined with each other. Also reviewed are retrospective subset analyses of the effect of a *KRAS* mutation on the response to anti-EGFR antibodies.

Methods: MEDLINE (2004–2009) was searched for randomized Phase II–III clinical trials of monoclonal antibodies in mCRC published in English. The search terms were *colorectal neoplasms*, *bevacizumab*, *cetuximab*, *panitumumab*, and KRAS *mutation*, alone or in combination. Information on the effect of *KRAS* mutation status on the response to anti-EGFR antibodies was drawn from retrospective subset analyses within the selected trials.

Results: The literature search identified 5 trials of bevacizumab in mCRC. Of these trials, 3 found a significant benefit on the primary end point (progression-free survival [PFS] or overall survival [OS]) when bevacizumab was added to chemotherapy, either as first-line (2 trials) or second-line (1 trial) treatment. The literature search identified 5 trials of cetuximab and 1 trial of panitumumab in mCRC. Of these trials, 4 found a significant benefit on the primary end point (response rate, PFS, or OS) with cetuximab or panitumumab as monotherapy or added to chemotherapy, either as first-line (1 trial) or later-line (3 trials) treatment. In all trials, the benefit of anti-EGFR therapy was limited to patients who had *KRAS* wild-type tumors. Of 3 identified trials of combined anti-EGFR and anti-VEGF therapy, 2 found that the combination of an anti-EGFR antibody and the anti-VEGF antibody bevacizumab had a significant negative effect on the primary end point (PFS) compared with no added anti-EGFR antibody.

Conclusions: In the studies reviewed, the anti-VEGF antibody bevacizumab added to chemotherapy and the anti-EGFR antibodies cetuximab and panitumumab as monotherapy or added to chemotherapy were associated with consistent efficacy in the treatment of mCRC, although the absolute benefit differed among trials. The efficacy of anti-EGFR antibodies was limited to patients with *KRAS* wild-type tumors. Given the lack of benefit when anti-VEGF and anti-EGFR antibodies were combined, such regimens should not be used in clinical practice. (*Clin Ther.* 2010;32: 437–453) © 2010 Excerpta Medica Inc.

Key words: metastatic colorectal cancer, targeted therapy, review, *KRAS* mutation.

INTRODUCTION

Colorectal cancer is the second most common cause of cancer death in the Western world, and its incidence is increasing.[1] Approximately 50% of patients eventually develop metastatic disease, for which palliative systemic treatment is usually administered.

The treatment options for patients with metastatic colorectal cancer (mCRC) have changed considerably in recent years. For several decades, 5-fluorouracil + leucovorin (5-FU/LV) was the only effective treatment regimen, associated with a median overall survival (OS) of ~12 months.[2] Oral fluoropyrimidines (capecitabine, uracil/ftorafur [UFT]) have been reported to be as effective as intravenous 5-FU/LV, with better tolerability.[3,4] For example, in a study in 1207 patients with

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mCRC, capecitabine was associated with a higher response rate (RR) compared with 5-FU (26% vs 17%, respectively; $P < 0.001$), with a comparable time to progression and OS.[5] The introduction of the cytotoxic agents irinotecan and oxaliplatin (OX) further improved median OS.[6,7] Prospective randomized studies found that combined administration of these agents was associated with no significant survival benefit compared with sequential use.[8–10] In a pooled analysis of data from 3494 patients treated with either capecitabine or 5-FU as part of an OX-containing regimen, the RR was significantly higher in the 5-FU/OX group compared with the capecitabine + OX (CAPOX) group (odds ratio = 0.85; $P = 0.02$), with no significant differences in progression-free survival (PFS) or OS between groups.[11] In some studies, the combination of capecitabine + irinotecan (CAPIRI) was associated with a greater incidence of grade 3–4 toxicity compared with the combination of 5-FU/LV + irinotecan (FOLFIRI),[12,13] although in the largest published study to date, use of CAPIRI was reported to be well tolerated.[8] Possible explanations for these discrepant results have been reviewed elsewhere.[14]

More recently, a new class of targeted agents has provided further benefit. Currently available targeted agents fall into 2 groups: monoclonal antibodies that bind to the ligand or the extracellular domain of a receptor, and small-molecule tyrosine kinase (TK) inhibitors that target the intracellular part (the TK domain) of a receptor. Both groups of targeted agents inhibit the signal transduction pathways through TK receptors that are necessary for cancer cell growth.[15] Activation of these transmembrane receptors leads to the stimulation of several intracellular signal transduction pathways, ultimately resulting in cell proliferation, dedifferentiation, inhibition of apoptosis, and stimulation of neoangiogenesis.[16] Several other targeted strategies for inhibition of intracellular signaling transduction molecules (eg, mTOR,[17] mitogen-activated protein kinase [MAPK],[18] multiple targets [sorafenib][19]) are in the early stages of development.

To date, 2 types of monoclonal antibodies have been approved by the US Food and Drug Administration and the European Medicines Agency for clinical use in mCRC: the anti–vascular endothelial growth factor (VEGF) receptor antibody bevacizumab* and the anti–epidermal growth factor receptor (EGFR) antibodies cetuximab† and panitumumab.‡

This article reviews the results of prospective randomized clinical trials of anti-VEGF and anti-EGFR antibodies in mCRC, either as monotherapy, combined with chemotherapy, or combined with each other. Because tumors harboring a mutation in the *KRAS* oncogene have been found to be resistant to anti-EGFR antibody therapy,[20–23] this article also reviews retrospective subset analyses of the effect of a *KRAS* mutation on the response to anti-EGFR antibodies.

METHODS

MEDLINE (2004–2009) was searched for randomized Phase II–III trials of monoclonal antibodies in mCRC published in English. The following search terms were used, alone or in combination: *colorectal neoplasms*, *bevacizumab*, *cetuximab*, *panitumumab*, and KRAS *mutation*. Abstracts of the retrieved publications were examined for relevance. The reference lists of selected articles were searched for additional relevant publications. Abstracts of meeting presentations were not included. Information on the effect of *KRAS* mutation status on the response to anti-EGFR antibodies was drawn from retrospective subset analyses within the selected trials.

MECHANISMS OF ACTION

The Vascular Endothelial Growth Factor Pathway

VEGF is the most potent angiogenic factor identified to date.[24] The VEGF family consists of 6 members, of which VEGF-A has been the most extensively studied. Members of the VEGF family exert their effect through binding to 1 of 3 VEGF receptors, which are localized predominantly on endothelial cells and angioblasts. Binding of VEGF to its receptor leads to activation of several intracellular signal transduction pathways. In addition, the VEGF receptor-2 has been found to be expressed on colorectal cancer cell surfaces in up to 50% of samples studied.[25] The production of VEGF-A is stimulated by hypoxia-inducible factor 1α and EGF.[26] In neoangiogenesis, the release of VEGF-A and other proangiogenic factors promotes degradation of the extracellular matrix,

*Trademark: Avastin® (Genentech Inc., South San Francisco, California).

†Trademark: Erbitux® (Merck KGaA, Darmstadt, Germany).

‡Trademark: Vectibix® (Amgen Inc., Thousand Oaks, California).