ANNALS OF GASTROENTEROLOGY 2007, 20(1):78-80

Lecture

Prevention and targeted treatment of colorectal cancer latest developments

N. Tsavaris

INTRODUCTION

Colorectal cancer (CRC) represents a major health problem in the Western world. Approximately 60% of patients with CRC require systemic therapy for metastatic disease, either at diagnosis or at disease recurrence. Development of systemic treatment for metastatic colorectal cancer (mCRC), starts from 1957 with 5-FU which was introduced and subsequently dominates the systemic treatment of mCRC, Until recently, classic chemotherapeutic agents have been combined in the treatment of advanced CRC. The molecular mechanisms involved in cancer biology and available technologies for drug discovery have prompted the development of new therapeutic tools targeting specific cancer-associated molecular pathways.

Among these so-called biological therapies, monoclonal antibodies (MAbs) have now reached the time of clinical application. Although, the use of MAbs in hematological malignancies have met with success, therapy of solid tumors faces many obstacles.

Recent considerable development of novel monoclonal antibodies that target key components of biological pathways has expanded the options to treat advanced mCRC patients. These newer agents more specifically target unique features of the cancer cell and its surroundings and so attempt to exploit the progress that has been made in the understanding of basic cell biology. Two targets in particular, the process of new blood vessel development, or angiogenesis, and the EGF receptor and its signalling pathway are exploited by the newest monoclonal antibodies available for use in this setting.[1]

Medical Oncologist, Assoc Prof University of Athens, School of Medicine

Author for correspondence:

N. Tsavaris, General University Hospital,
Department of Pathophysiology,
115 27 Athens, Greece, e-mail: tsavaris@med.uoa.gr

The HER family of transmembrane tyrosine kinase growth factor receptors has provided targets for serotherapy in solid tumors. Interaction of peptide growth factor ligands with HER family receptors triggers signaling through the Ras-mmitogen-activated protein kinase pathway and phosphatidylinositol 3kinase pathways, enhancing cell cycle progression, proliferation, and survival in normal cells and cancer cells. Of the four HER family receptors, most attention has been given to HER-1 (epidermal growth factor receptor) and to HER-2. MAbs used in solid tumors (Trastuzumab, cetuximab and bevacizumab) have increased the efficacy of treatment of some of them with acceptable adverse events.[2]

Monoclonal antibodies in colorectal cancer have targeted two major signalling pathways critical to oncogenesis: i. the epidermal growth factor receptor (EGFR) and ii. vascular endothelial growth factor (VEGF)

These antibodies showed clinical activity in mCRC, especially when combined with chemotherapy.

Cetuximab (IMC-Cn5)

Several monoclonal antibodies have been prepared against the extracellular domain of the l70-kDa epidermal growth factor receptor (EGFR) that is overexpressed in a number of carcinomas, including non-smaIl-cell lung cancer, head and neck cancer, pancreatic cancer, and some 70% of colorectal cancers. Cetuximab is a humanized monoclonal antibody that blocks the ligand-binding site of EGFR, preventing receptor activation and signaling. In experimental systems, treatment of human cancer cells with cetuximab produces cell cycle arrest in G0-G1, induces p21, directs hypophosphorylation of Rb, inhibits proliferation, and blocks the production of angiogenic factors such as vascular endothelial growth factor (VEGF).[3] In addition, treatment with cetuximab potentiates the activity of doxorubicin, paclitaxel, topotecan, and irenotecan in nude mouse heterografts of human cancer. In a phase II

trial a combination of irinotecan and cetuximab was used to treat patients with documented metastases from EGFR-positive colorectal cancer that had previously been treated with irinotecan.[4] Cetuximab and irinotecan produced a partial response in 21 of 121 patients (17%), with a median duration of 84 days. Interestingly, the level of EGFR expression did not correlate with response to the combination. Promising Phase II trials have also been conducted in head and neck cancer and in pancreatic cancer.[5,6]

Anti-Endothelial and Anti- VEGF Antibodies

Over 30 years ago, it was proposed that blocking new blood vessel formation would significantly inhibit solid tumor growth and hence, limit cancer progression. Efforts guided by this philosophy have resulted in a better understanding of the molecular basis of tumor angiogenesis. The first successful therapy to emerge from this work, an antibody (bevacizumab) targeting the vascular endothelial growth factor (VEGF), was recently approved for the treatment of colorectal cancer.

Angiogenesis is critical for normal fetal growth and wound healing, but it is also required for tumor growth and metastasis.[7] Novel approaches to inhibiting angiogenesis have exploited the presence of antigens displayed on tumor-associated endothelium or on pro-angiogenic factors produced by tumor cells. Endoglin and endosialin are two endothelial cell surface antigens that are preferentially expressed on proliferating vascular cells and might be exploited as targets for cytotoxic therapy.[7] Other angiogenic markers identified so far include three domains of fibronectin, which are overexpressed in tumor-derived cells: IIlCS, ED-A, and ED-B.[8]

Blockade of VEGFs or their receptors can inhibit tumor-driven angiogenesis in heterograft models.[9] VEGF is identical to vascular permeability factor (VPF), and expression of VEGF/VPF has correlated with formation of ascites in ovarian cancer heterograft models.[10] Treatment of mice bearing human ovarian heterografts with anti- VEGF antibody can completely inhibit ascites formation.[11] Recombinant humanized anti- VEGF antibody has been well tolerated in phase I clinical trials, with only 3 episodes of bleeding observed among 25 patients treated.[12]

Bevacizumab plus 5FU/LV has resulted in higher response and longer survival than 5FU/LV alone in first line metastatic colorectal cancer; its combination with oxaliplatin has recently doubled results. Additional positive clinical data with bevacizumab in the treatment of breast and lung carcinoma have also been reported.[13]

CONCLUSION

These clinical achievements have validated the approach of anti-angiogenesis therapy for cancer and provided further confirmation for antibodies as a therapeutic class in this disease. Nevertheless, important unanswered questions with regard to preclinical and clinical results of VEGF pathway inhibitors remain. For example, preclinical models with a number of VEGF pathway inhibitors suggest that these agents would have significant clinical activity on their own; yet, clinical activity in patients with bevacizumab or other VEGF pathway inhibitors as monotherapy have been disappointing. Moreover, while bevacizumab is approved for the treatment of colorectal cancer in combination with cytotoxics, the mechanism for the benefits of this combination are still poorly understood, with a number of viable mechanisms under active experimental evaluation. The 3-8-month survival benefit in colorectal cancer patients treated with bevacizumab is a positive step forward. However, improving our understanding of the mechanism for these effects, as well as the mechanism underlying the inability as yet to achieve greater effects, is needed in order to follow up on the positive clinical results with improved strategies. This review discusses the experimental results surrounding the current status of our understanding of the mechanism of action of VEGF signaling inhibitors, and the potential for utilizing these agents in the future so that clinical benefits will be measured in years rather than months.[13]

The superior therapeutic efficacy of these molecular targeting agents over traditional chemotherapy has been shown by the survival benefit achieved by patients with advanced or recurrent cancers. Although the precise molecular mechanism by which these agents produce or enhance an antitumour effect, alone or in combination with anticancer drugs, is unknown, the specific inhibition of target genes critically involved in tumour progression and metastasis is clear. Further studies to determine which patient groups and anticancer drugs are more appropriate for combination therapy with these agents are needed. All the most important data obtained through recent studies are discussed, emphasizing their mechanisms of action, safety profiles and clinical applications.[14]

REFERENCES

1. Vincenzi B, Schiavon G, Silletta M, Santini D, Tonini G. The new era in the treatment of advanced colorectal cancer patients: the role of monoclonal antibodies. Expert Opin Emerg Drugs. 2006;11: 665-683.
2. Kalofonos HP, Grivas PD. Monoclonal antibodies in the

management of solid tumors.Curr Top Med Chem. 2006; 6:1687-705.
3. Mendelsohn. J. Targeting the epidermal growth factor receptor for cancer therapy. J Clin Oncol 2002; 20:1-13.
4. Saltz L, Rubin M, Hochster H, et at. Cetuximab (IMCC225) plus irinotecan (CPT-11I) is active in CPT II, refractory colorectal cancer (CRC) that expresses epidermal growth fador receptor (EGFR). Proc of ASCO, 2001; 30:3a (7).
5. Herbst RS, Hong WK. IMC-225,an antiepidermal growth factor receptor monoclonal antibody for treatment of head and neck cancer. Semin Oncol 2002; 29: 18-30.
6. Abbruzzese JL, Xiong HQ. Epidermal growth factor receptor-targeted therapy for pancreatic cancer. Semin in OncoI 2002; 29:31-37.
7. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nature Medicine 1995; 1:27-31.
8. Rettig WJ, Garin-Chesa P, Healey JH, et al. Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer. Proc Natl Acad Sci USA 1992;89:10832-10836.
9. Zardi L, Carmonella B, Siri A, et al. Transformed human cells produce a new fibronectin isoform by preferential alternative splicing of a previously unobserved exon. EMBO J 1987; 6:2337- 2342.
10. Skobe M, Rockwell P, Goldstein N, et al. Halting angiogenesis suppresses carcinoma cell invasion. Nat Med 1997; 3:1222-1227.
11. Yoneda J, Kuniyasu 1-1, Crispens MA, et al. Expression of angiogenesis-related genes and progression of human ovarian carcinomas in nude mice. J Natl Cancer Inst 1988; 90:44754.
12. Mesiano S, Ferrara N. Jaffe RB. Role of vascular endothelial growth factor in ovarian cancer. Am J Pathol 1998; 153:1249-1256.
13. Tonra JR, Hicklin DJ. Targeting the vascular endothelial growth factor pathway in the treatment of human malignancy. Immunol Invest. 2007; 36:3-23
14. Pasetto LM, Bortolami A, Falci C, Sinigaglia G, Monfardini S. Recent progress in target therapy in colorectal cancer. Anticancer Res. 2006; 26(5B):3973-3981