Chapter 7

CONTINUOUS INHIBITION OF ANGIOGENESIS IN RAS MUTANT COLORECTAL CANCER: A REVIEW

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INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide. For patients with stage IV disease, the aim of the treatment is to prolong survival with sustained quality of life.

Angiogenesis plays a critical role in colorectal cancer progression. The major factor controlling angiogenesis is vascular endothelial growth factor (VEGF). Inhibition of VEGF produces a significant antitumor response therefore anti-angiogenic agents are currently the standard of care in mCRC patients. Bevacizumab, aflibercept, regorafenib and ramucirumab have improved progression free and overall survival (PFS, OS) rates in different lines of treatment.

By the introduction of targeted therapies substantial progress in the management metastatic colorectal cancer (mCRC) has been obtained. It has been established that application of all avaliable agents in the course of disease provides survival improvement of more than thirty months. However the optimal duration of initial chemotherapy for mCRC is unknown and prolonged period of chemotherapy is associated with cumulative toxicities including neuropathy, steatohepatitis and impaired psychosocial function. Recently, a considerable literature has grown up around the theme of developing less toxic maintenance strategies without compromising of survival.

In literature there are several studies evaluating the role of maintenance therapy with less intensive regimens in patients who experienced disease response or stabilization following induction therapy as a strategy to decrease toxicity and improve quality of life.

This review is focused on the maintenance therapy with agents targeting VEGF and importance of continuous antiangiogenic inhibition in the course of mCRC.

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Other anti-VEGF agents including aflibercept, ramucirumab and regorafenib expands the anti-angiogenetic treatment options and demonstrates the advantage of continuous blockade of angiogenesis in the management of mCRC patients, however optimal sequencing strategy and the cost effectiveness of these anti-VEGF agents in the management of mCRC is still a matter of debate.

Despite the fact that targeting angiogenesis in patients previously exposed to anti-VEGF improves overall survival, we need biomarkers to rationalize our therapeutic strategies. In addition to clinical markers such as previous response, toxicity profile and patients' prefences; the cost of anti-angiogenic therapies is an important factor in determining the treatment regimen because of similar efficacy results. Biomarkers predicting the benefit from VEGF inhibition should be added into clinical trials to identify the effective agents that increase survival rates while reducing cost and toxicity.

Together with a considerable amount of literature already published, we support the continuous use of anti-angiogenic agents for patients with mCRC. Further exploratory analyses are required to identify the patients that are most likely to benefit from maintenance strategy.

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