

Abstract

Introduction: In recent years, significant progress has been made in the treatment of metastatic colorectal cancer (mCRC) due to the use of targeted therapy. Bevacizumab is a monoclonal antibody (mAb) against vascular endothelial growth factor (VEGF) and cetuximab and panitumumab are monoclonal antibodies against epidermal growth factor receptor (EGFR). MicroRNAs (miRs) are single-stranded non-coding RNA chains of 18-25 nucleotides in length that are involved in the regulation of gene expression and thus significantly influence the biological behaviour of cancer cells. Dysregulations at the miR level are considered promising candidates for prognostic and predictive biomarkers.

Aims: The aim of this work, divided into two parts, was to evaluate the association of dysregulation of selected miRs with the effect of targeted therapy in patients with mCRC.

Methods: The first study included 63 mCRC patients treated with chemotherapy and bevacizumab. The second study included 46 mCRC patients treated with chemotherapy and cetuximab or panitumumab. Assessment of treatment effect included progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and disease control rate (DCR). Samples of frozen tumor and adjacent non-tumor tissue obtained during primary tumor surgery were used for analysis. The relative expression of microRNAs was measured by quantitative polymerase chain reaction (qPCR).

Results: In the first study, we observed down-regulation of miR-126-3p ($p < 0.0001$), miR-126-5p ($p < 0.0001$) and miR-664-3p ($p = 0.0132$) in tumor tissue. PFS and OS were significantly shorter in patients with down-regulation of miR-126-3p in tumor ($p = 0.0064$ and $p = 0.0027$) when treated with bevacizumab. In the second study, we observed down-regulation of miR125b ($p = 0.023$) and let-7c ($p = 0.004$) and up-regulation of miR17 ($p < 0.001$) in tumor tissue. We observed significantly lower ORR and DCR in patients with down-regulation of miR-125b in the tumor ($p = 0.0005$ and $p = 0.0383$), and after optimizing the stratification threshold, there was an association with shorter PFS and OS ($p = 0.055$ and $p = 0.006$) when treated with anti-EGFR targeted therapy. Furthermore, there was a significant association of down-regulation of let-7c with lower DCR ($p = 0.0255$).

Conclusions: Down-regulation of miR-126-3p in the tumor is associated with poor outcome of mCRC patients treated with chemotherapy and bevacizumab. Down-regulation of miR-125b and let-7c in the tumor is associated with poor outcome of wtRAS mCRC patients treated with chemotherapy and anti-EGFR targeted therapy. These miRs represent potential predictive biomarkers for targeted therapy of mCRC and their role should be further investigated.