The Role of Biologicals in the Management of Metastatic in Colorectal Cancer

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The management of patients with metastatic colorectal cancer (CRC) has changed dramatically over the last years, with increasing chances of prolonged survival. The median survival of patients with unresectable metastatic disease approaches now 24 months. The development of new cytotoxic and targeted agents; as well as the multidisciplinary management of patients with resectable and initially non-resectable metastases contribute to the progress. The development of the cytotoxic agents irinotecan, oxaliplatin and capecitabine and of the biological agents bevacizumab, cetuximab and panitumumab has clearly increased the therapeutic options for patients with metastatic colorectal cancer. Several other new agents are far advanced in development in colorectal cancer. Resection of liver- or lung metastases can lead to cure of patients with metastatic colorectal cancer. Complete resection of metastases leads to long term survival rates of 30-40%. Due to more active new combination regimens, some patients with initially unresectable liver metastases can also be downsized to resectable disease, leading to chances for cure in these patients.

The new targeted agents have been introduced recently in the therapeutic regimens of patients with metastatic colorectal cancer. There is a strong preclinical and clinical rationale for the use of Vascular Endothelial Growth Factor (VEGF) inhibitors in colorectal cancer. The anti-VEGF monoclonal antibody, bevacizumab, increases the activity of a variety of active cytotoxic regimens in metastatic CRC. It has been shown in randomized phase 3 trials that bevacizumab, when combined with irinotecan plus 5-fluorouracil (5-FU)/ leucovorin (LV) in the first-line treatment of metastatic CRC and with FOLFOX (5-FU/LV/oxaliplatin) in second-line treatment leads to an increased median survival, progression-free survival (PFS) and response rate (RR) compared to the cytotoxic chemotherapy alone. Moreover, it has been demonstrated in a few randomized phase 2 studies and in a combined analysis of these phase 2 studies that bevacizumab increases the activity of 5-FU/LV in the first-line treatment of metastatic CRC.

A large randomized phase 3 study of FOLFOX or capecitabine/oxaliplatin ± bevacizumab in the first-line treatment shows that capecitabine is as effective as IV 5-FU/LV when combined with oxaliplatin and that bevacizumab increases the PFS of the fluoropyrimidine/oxaliplatin combination. Based on these data it is today accepted that bevacizumab increases the activity of the different cytotoxic agents when these agents are combined. Bevacizumab is safe in colorectal cancer. It does not increase the typical chemotherapy related side effects, but is has some specific side effects: arterial hypertension, proteinuria, mucosal bleeding (most frequently epistaxis), arterial thromboembolic events, seldom gastrointestinal perforation and also wound healing problems.

Aflibercept (VEGF trap) is engineered soluble receptor made from extracellular domains of VEGFR1 and VEGFR1, binds to all isoforms of VEGF and to placental growth factor. Aflibercept is under active investigation in phase 3 in combination with standard cytotoxic combinations in metastatic CRC. Several small molecule VEGFR tyrosine kinase (e.g. cediranib, sunitinib, axitinib) are actually in phase 3 development in combination with standard combination cytotoxic regimens in metastatic CRC.

The anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab are also active in metastatic CRC. The activity has been shown initially in chemotherapy refractory metastatic CRC. The combination of cetuximab with irinotecan is more active in this setting than cetuximab alone. The activity of anti-EGFR antibodies is confined to patients with a KRAS wild type tumour. Recent data showed also an increased PFS of cetuximab in combination with chemotherapy in less advanced stages of metastatic CRC. The PFS of the combination FOLFIRI/ cetuximab was significant longer than that of FOLFIRI alone in a phase 3 trial in the first line treatment of CRC and of cetuximab/irinotecan compared to irinotecan alone in the second line treatment of metastatic CRC. It has recently been shown that the activity of the anti-EGFR antibodies is confined to patients with a KRAS wild type tumor and it is known that +/- 60 % of patients with colorectal cancer have a KRAS wild type tumor.

Many open questions and challenges remain in relation to the use of the anti-VEGF and anti-EGFR antibodies in metastatic CRC. Answers are needed to optimize the outcome for patients and the more optimal use of the resources. A crucial challenge is to demonstrate which patients are more likely to respond to bevacizumab-containing regimens and to the anti-EGFR antibodies cetuximab and panitumumab. The mentioned data on KRAS as a predictor for activity are very important and are certainly the beginning of a new era of in the management of CRC. They help us to predict which patients will not benefit from cetuximab and panitumumab. Further research is needed to determine which markers will help us to predict the activity of cetuximab and panitumumab on top of the KRAS status and also to find predictive markers for angiogenesis inhibitors.

A second important challenge is the strategic question on the best combination, on the best sequence and on the most optimal use of the different cytotoxic agents in combination with the biologicals in CRC. Amongst other relevant clinical questions are questions on the optimal duration of bevacizumab, on the continuation of bevacizumab after progression, on the significance of skin rash in patients treated with anti-EGFR antibodies and on the real impact of bevacizumab and cetuximab in the neoadjuvant preoperative treatment of liver metastases. An important challenge is the understanding of the mechanism why tumours that initially respond to a combination of cytotoxics and biologicals may become resistant to this combination.

In conclusion: the management of patients with advanced colorectal cancer has improved. The introduction of the classic cytotoxic agents, as well of the targeted agents contributed to the progress. The angiogenesis inhibitor, bevacizumab, as well as the EGFR inhibitors have clearly increased the therapeutic armentarium of patients with metastatic colorectal cancer. The introduction of the new agents offer also prospects for an increased chance of a longer survival for patients with metastatic colorectal cancer. The major challenge is now to implement strategies in which patients can be selected, based on molecular characteristics and/or pharmacogenomic profiles so that the new drugs and the resources can be used optimally for our patients with metastatic colorectal cancer.