Poly-chemotherapy +/- monoclonal antibodies (mAbs) to VEGF (bevacizumab) or EGFR (Cetuximab and Panitumumab in wt-kras patients) represents the standard treatment for metastatic colon cancer patients (mCRC), with a median overall survival (OS) of 22-28 months. More recently, a better understanding of cancer pathogenesis and immune-system has provided new treatment options for these patients, including targeted agents and immunotherapy. Due to their malignant phenotype, tumor cells express immunogenic structures and mutated proteins and therefore, they may be killed by activated cytotoxic-T-lymphocytes (CTLs). These effectors recognize antigen-derived peptides (epitopes), bound to class-I HLA molecules on their membrane. In this context, a number of antigen-epitopes (derived by CEA, MUC-1, telomerase, and thymidylate synthase) able to generate a systemic immune-response with antitumor activity in preclinical studies, have already been tested in a number of different explorative trials in mCRC. More recently, a critical role for systemic inflammation, tumor microenvironment and inhibitory immune-check points in allowing tumor immune-escape has been recognized. Thus new biological constructs and combination strategies have been evaluated in order to improve the immune-reactivity, CTL expansion and immune-rejection. Clinical trials have been designed to test recombinant DNA or viral constructs engineered to express CEA / MUC1 gene, co-accessory and adhesion molecules; mAbs to inhibitory immune-check points CTLA4, and PD-1; immunomodulating cytotoxic drugs and immunoadjuvant cytokines (aldesleukine and GM-CSF). In this context, the positive results of the GOLFIG2 phase III trial, that showed, the superiority of chemo-immunotherapy (gemcitabine-oxaliplatin, 5-Fluorouracil followed by GMCSF and aldesleukine) over FOLFOX-4 chemotherapy in first-line mCRC patients, open a new realistic research area for the treatment of mCRC.

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