Current standards and new trends in the primary treatment of colorectal cancer

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Early colon cancer

Despite increasing availability of drugs in the metastatic setting, adjuvant treatment for stage II and III colon cancer is still based on fluoropyrimidines (FP) with or without oxaliplatin. Although the results of the last cetuximab-based trial (PETACC 8) are still pending, further development of adjuvant use of cetuximab and bevacizumab after the results of NO147, NASBP C-08, and AVANT seem unlikely. Instead, current research focuses on prognostic and predictive markers for tailoring treatment, particularly in stage II disease. Determination of MSI/MMR status for prediction of benefit from single-agent 5FU and gene array analyses are currently being investigated, although data are not mature and are even conflicting [1–3].

Decisions on adjuvant treatment need to be discussed with the patient on an individual basis taking into account patient characteristics (performance status, age, co-morbidity and individual preferences) as well as tumour features (pathological stage, grading and overall risk of relapse). Adjuvant treatment should be administered as soon as possible after resection for up to six months. High-risk (HR) stage II patients, defined by at least one of the following clinical risk factors should receive adjuvant chemotherapy with single-agent FP: lymph node sampling <12, poorly differentiated tumour, vascular or lymphatic or perineural invasion, obstruction or perforation or pT4 stage. Adding oxaliplatin in HR stage II patients showed a non-significant trend towards increased disease-free survival (DFS), without affecting overall survival (OS) in the MOSAIC trial [4]. Patients with stage II disease without risk factors might still be treated with adjuvant FP. Adjuvant treatment with a combination of FP and oxaliplatin (FOLFOX, XELOX) should be offered to all eligible patients with stage III disease. Single-agent FP is an option if oxaliplatin has to be avoided. Particularly, physically fit patients older than 70 years (biological age) with stage III disease should receive adjuvant chemotherapy with single-agent FP.

Colorectal cancer with synchronous metastases

Management of synchronous disease is changing in terms of leaving an asymptomatic primary tumour in situ and starting with upfront systemic (and/or local) treatment pursuing a curative approach for potentially resectable disease (liver and/or lung metastases) and avoiding mutilating surgery in unresectable disease.

Colorectal cancer with resectable liver and/or lung metastases

Patients presenting with resectable liver and/or lung metastases should undergo resection and/or multimodal management in order to decrease recurrence rates. Post- and/or preoperative systemic chemotherapy with FP and/or oxaliplatin shows a trend towards a benefit regarding progression-free (PFS) and overall survival (OS), without increasing postoperative complication rates. Since all available trials failed to show a statistically significant improvement, no broadly accepted standard treatment exists. Currently ongoing trials evaluate the addition of further agents, e.g. cetuximab, bevacizumab and/or irinotecan to perioperative FP and oxaliplatin.

Metastatic colon cancer

The selection of a specific first-line treatment is dependent on the clinical presentation and biology of the tumour (metastases limited to liver and/or lung, presence of peritoneal metastases, dynamics of progression, symptoms) and patient characteristics (co-morbidity, eligibility for secondary resection) and drug-related factors (availability, predictive markers).

KRAS mutation, which excludes patients from treatment with anti-EGFR antibodies, is the only relevant predictive molecular marker for treatment decision at the moment. Despite the strong adverse prognostic information of *BRAF* mutation, the predictive value of treatment with anti-EGFR antibodies is not clear [5,6]. Although not prospectively proven, achievement of a disease-free or no evidence of disease (NED) status after chemotherapy, surgery and/or locally ablative techniques (e.g. radiofrequency ablation) offers the potential of long-term survival or cure in an otherwise palliative situation. While this applies particularly to liver and lung metastases, it might also be the case for limited peritoneal disease.

The most active induction chemotherapy should be chosen for all potential NED-amenable patients. Patients with symptomatic, aggressive disease should receive an active two- to three-drug regimen as first-line treatment. Single-agent treatment (or even watchful waiting) might be still considered in patients with low tumour burden, indolent and asymptomatic disease, in the case of fully informed consent and close monitoring.

Choice of regimen

Treatment regimens with highest response rates in phase III trials are combination chemotherapy with EGFR inhibitors for *KRAS* wild-type and FOLFOXIRI. With respect to current data oxaliplatin-based chemotherapy combined with cetuximab and oral or bolus FP (e.g. XELOX or FLOX) should be avoided [7,8]. Irinotecan or oxaliplatin-containing FP (FOLFIRI, XELIRI, IFL, FOLFOX, XELOX) combinations with or without bevacizumab are possible options as well. For asymptomatic, unresectable, or co-morbid patients single-agent FP with or without bevacizumab represents a reasonable alternative. Four drug combinations with FP, irinotecan and oxaliplatin combined with either cetuximab/panitumumab or bevacizumab are currently investigated, with high response and disease control rates in single arm phase II trials.

Treatment duration

Treatment should be continued according to the individual situation, patient's needs, cumulative toxicity (in particular neurotoxicity with oxaliplatin) and aggressiveness of the disease. Survival is not relevantly impaired if first-line combination treatment with all drugs is not given continuously until progression. If secondary resection is either not possible owing to patient factors or not feasible owing to disease characteristics, continuation of combination chemotherapy (in particular oxaliplatin) beyond 3–4 months is not recommended. Maintenance treatment might be considered, especially in patients with aggressive disease [9,10]. However, in the case of progression during treatment-free periods the same treatment should be reinstituted, if feasible. Pre-planned treatment intervals and break duration ("intermittent treatment") or discontinuation after 3–4 months and restart of treatment in the case of progression, "stop and go" are further options. Results of the ongoing CAIRO3 and AIO 0207 may help in defining the use of maintenance versus observation after 4.5–6 months of induction chemotherapy.

Current sequential approaches, comparing single agents with upfront combinations (CAIRO, FOCUS, LIFE) show improved response and PFS with upfront combination treatment, and similar OS for both approaches, and may therefore be an option for patients not requiring tumour shrinkage.

Conflict of interest statement

A. Stein and D. Atanackovic have no conflict of interest to declare. C. Bokemeyer reports participating in advisory boards for Merck Serono and receiving honoraria and research funding from Roche and Merck Serono.

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