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Advanced colorectal cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

In 2006 there were 412 900 new cases of colorectal cancer in Europe. This is 12.9% of all cancer cases. Colorectal cancer was responsible for 217 400 deaths in Europe in 2006. This represents 12.2% of all cancer deaths. Approximately 25% present with metastases at initial diagnosis and almost 50% of patients with colorectal cancer will develop metastases.

diagnosis

Suspicion of metastatic disease should always be confirmed by adequate radiologic imaging, usually a computed tomography (CT)-scan and/or ultrasonography of the liver and plain chest X-ray.

In general, the first appearance of metastases should be cytologically or histologically confirmed. Only when there is a very typical presentation (imaging fully compatible with metastases in liver and/or lungs), high-risk stage at diagnosis, and interval since primary within 2–3 years, may this be omitted. Evaluation of the general condition, organ function and concomitant pathology determines the therapeutic strategy of patients with metastatic colorectal cancer.

staging and treatment strategy

In order to identify patients with metastatic colorectal cancer for which potentially curative surgical options are available the staging should include at least clinical examination, liver and renal function tests, carcinoembryonic antigen (CEA), CT-scan of the abdomen and chest. The general condition of the patient (including performance status) is a strong prognostic and predictive factor. Additional examinations, as clinically needed, are recommended prior to major abdominal or thoracic surgery with potentially curative intent. An FDG-PET can give additional information on unequivocal lesions before resection of metastatic disease or can identify new lesions in case of planned resection of metastases.

The selection of the optimal strategy should be discussed in a multidisciplinary team, especially if potentially resectable metastases are diagnosed.

treatment

Surgical resection should be considered for solitary or confined liver or pulmonary metastases.

After complete resection (R0) of metastases (liver or lung) the 5 year survival amounts to 25–35% (II, A). There is no role for partial palliative resection of metastases. Radiofrequency ablation, in combination with systemic treatment, is under investigation as an alternative or a complement to surgical resection of liver metastasis in cases where this is not possible or complete.

In patients with resectable liver metastases, perioperative combination chemotherapy with 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX regimen) slightly improves the progression-free survival by 7–8% at 3 years (I, B). The perioperative chemotherapy is given during 3 months (six cycles) before and 3 months after the surgical resection of the metastases.

Initially unresectable liver metastases can become resectable after downsizing with chemotherapy and, if so, resection should be considered after multidisciplinary discussions (diminution of the metastases in number only should not be considered as the majority of metastases in complete radiological remission still contain microscopic viable tumor cells). Combination chemotherapy is advisable in patients with potentially resectable metastases. Scarce data on the combination of the three cytotoxics suggest an increased resection rate after the combination of 5-FU, oxaliplatin and irinotecan, although concerns on toxicity limit the use of this regimen to highly selected cases. The combination of two cytotoxics with cetuximab (in KRAS wild-type patients) or with bevacizumab seem to increase the resection rate of initially unresectable liver metastases.

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First line palliative chemotherapy consists of a fluoropyrimidine (i.v. 5-fluorouracil (5-FU) or oral fluoropyrimidines) in various combinations and schedules. Infused regimens of 5-FU/leucovorin (LV) are generally less toxic than bolus regimens. The oral fluoropyrimidines capecitabine and uracil-ftorafur (UFT)/LV are an alternative to intravenous 5-FU/LV as monotherapy but their relative activity and safety to infusional 5-FU has not been established.

Combination chemotherapy with 5-FU/LV/oxaliplatin (FOLFOX) or 5-FU/LV/irinotecan (FOLFIRI) provides higher response rates, longer progression-free survival and better survival than 5-FU/LV (I, B). FOLFOX and FOLFIRI have a similar activity, but a different toxicity profile: more alopecia and febrile neutropenia for irinotecan and more polyneuropathy for oxaliplatin (I, B). Two studies ('FOCUS' and 'CAIRO') showed that combination chemotherapy was not superior to sequential treatment in terms of overall survival, and therefore sequential therapy starting with fluoropyrimidine monotherapy remains a valid treatment option in selected and frail patients (I, B). Nevertheless, when an objective response is the primary goal in a specific patient (for instance, in view of surgical resection of metastases), combination chemotherapy remains the preferred option (IV). The exposure of all three cytotoxics (fluoropyrimidines, oxaliplatin and irinotecan) in various sequences, results in the longest survival.

The combination of capecitabine plus oxaliplatin (CAPOX) is an alternative to infused 5-FU and oxaliplatin (FOLFOX) [I, A] similar activity compared to the combination of 5-FU, LV and oxaliplatin. The original 3 weekly regimen of capecitabine/irinotecan (2000 mg/m^2/d and irinotecan 250 mg/m^2 q3 w) seems to be more toxic than 5-FU/LV/irinotecan. This regimen is therefore less well established and less frequently used in its original form. A dose reduced regimen seems be less toxic, while maintaining the activity.

The duration of chemotherapy for metastatic colorectal cancer remains controversial. Options are a fixed treatment period and treatment until progression or toxicity. Treatment interruptions of combination chemotherapy or less intensive cytotoxic treatment can be considered if cumulative toxicity occurs and if disease control is reached. A maintenance treatment with a fluoropyrimidine alone prolongs the progression-free survival compared to a complete treatment break after an initial period of combination chemotherapy (I, B). Reintroduction of combination chemotherapy is usually indicated in case of progression.

Second line chemotherapy should be proposed for patients with good performance status. In patients refractory to fluoropyrimidine monotherapy, second line must consist of a combination with xaliplatin or irinotecan. In patients refractory to FOLFOX, an irinotecan based regimen is proposed in the second line treatment. In patients refractory to FOLFIRI, FOLFOX is proposed in the second line treatment.

Bevacizumab, an anti-VEGF antibody, should be considered in patients with metastatic colorectal cancer, as it increases the survival and progression-free survival in the first line treatment in combination with 5-FU/LV and irinotecan and in combination with 5-FU/LV alone (I, B). Bevacizumab improves the survival and progression-free survival in combination with FOLFOX in the second line treatment (I, B). Bevacizumab improves also the progression-free survival in combination with a fluoropyrimidine plus oxaliplatin in the first line treatment of metastatic colorectal cancer (I, B). Bevacizumab has specific class effect side effects: hypertension, proteinuria, arterial thrombosis, mucosal bleeding, gastrointestinal perforation and wound healing. Patients older than 65 years with a history of arterial thrombotic events are at significant higher risk for having an arterial thrombosis while treated with bevacizumab. There are no validated predictive molecular markers available for bevacizumab.

The anti-EGFR antibodies cetuximab and panitumumab are active as single agent in chemoresistant metastatic colorectal cancer. It has been shown that cetuximab improves the survival of chemoresistant patients compared to Best Supportive Care (BSC). Panitumumab single agent improved the progression-free survival compared to BSC (I, B). The panitumumab trial did not show a survival difference due to the cross-over design of the trial. The combination of cetuximab with irinotecan is more active than cetuximab monotherapy in chemoresistant patients. Combination data of cytotoxics with panitumumab are lacking in chemoresistant patients. The activity of cetuximab and panitumumab is confined to patients with a KRAS wild-type tumor (II, A). The anti-EGFR antibodies should not be used in patients with a KRAS mutated tumor. The combination of cetuximab and irinotecan has become the reference treatment in chemoresistant KRAS wild-type tumors who can tolerate the combination.

The activity of FOLFIRI is increased in the first line treatment when cetuximab is combined to FOLFIRI and FOLFOX in KRAS wild-type patients.

The anti-EGFR antibodies induce in most treated patients an acneiform rash. Hypomagnesemia is another class specific side effect. Cetuximab is a chimeric antibody that gives slightly more frequent allergic reactions than the human monoclonal antibody panitumumab.

response evaluation

History, physical examination, CEA if initially elevated, and a CT-scan of the involved region are recommended after 2–3 months of palliative chemotherapy (IV).

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