

Symposium 5

Down Staging Chemotherapy and Appropriate Timing of Resection in CRLM

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The majority of patients have metastatic disease that initially is not suitable for resection. It is, however, important to select patients in whom the metastases are suitable for resection and those with initially unresectable disease in whom the metastases can become suitable for resection after a major response has been achieved with combination chemotherapy. The aim of the treatment in the last group of patients may therefore be to reverse initially unresectable metastatic CRC to resectable CRC.

The optimal treatment strategy for patients with clearly unresectable metastatic CRC is rapidly evolving. The treatment of patients should be seen as a continuum of care in which the determination of the goal of the treatment is important: prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life. The outcome of patients with metastatic CRC has clearly improved during the last years with median survival now reaching almost 24 months.

Surgical resection should be considered for solitary or confined liver metastases, since it offers patients with metastatic CRC the best chance of long-term survival with actuarial 5-year survival rates (following hepatic resection) ranging from 30~35% to >50% in some selected series. Unfortunately, 60~75% of these patients will suffer a relapse following resection of their hepatic metastases, with the majority occurring in the liver. 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 metastases in cases where this is not possible or complete.

In patients with resectable liver metastases, perioperative combination chemotherapy with the FOLFOX

regimen improves the progression-free survival by 7~8% at 3 years. The perioperative chemotherapy is given for 3 months (six cycles) before and 3 months after the surgical resection of the metastases. In the case that no preoperative chemotherapy can be or has been administered, postoperative adjuvant treatment with FOLFOX should be considered. There is no evidence yet that adding a biological to a cytotoxic doublet improves the outcome in resectable metastases compared with a cytotoxic doublet alone in combination with resection of the metastases. Resection of resectable lung metastases offers also 25~35% 5-year survival rates in carefully selected patients.

Initially unresectable liver metastases can become resectable after downsizing with chemotherapy and, if so, resection should be considered after multidisciplinary discussions. For patients with initially unresectable liver metastases, a strong correlation between response rate and resection rate in the neoadjuvant treatment of metastatic CRC has been demonstrated. Pathological response seems to be a surrogate for predicting the outcome. Thus, the strategy when treating patients with initially unresectable disease is to try to achieve high response rates in order to convert unresectable metastases to resectable metastases. Diminution of the metastases in number only should not be considered as the majority of metastases in complete radiological remission still contain microscopic viable tumour cells. In patients in whom the metastases have disappeared on standard imaging, microscopic disease is often still present and a multidisciplinary discussion for the optimal strategy has to take place. Standard combination chemotherapy regimens comprising 5-FU/LV in combination with either irinotecan, typically FOLFIRI, or oxaliplatin (FOLFOX) have been reported to facilitate the resection of 7~40% of patients with

initially unresectable metastases depending upon the initial selection of patients. However, 75~80% of these patients experience cancer relapse within 2 years of resection. Data emerging from randomized trials suggest that the addition of a targeted agent (bevacizumab or cetuximab) or even scarce data of phase II trials on the combination with a third cytotoxic plus or minus a targeted agent, might be even more effective, although concerns about toxicity limit the use of this triple cytotoxic regimen to highly selected cases. The combination of a doublet of cytotoxics plus cetuximab has led to higher resection rates (although still low in absolute numbers) in patients with liver limited unresectable metastatic KRAS wild type CRC. The combination of FOLFOX/cetuximab and FOLFIRI/cetuximab has led to similar response rates and resection rates in KRAS wild-type tumours. The combination of a fluoropyrimidine/oxaliplatin/bevacizumab has led to a non-significant trend in an increased resection rate compared with the cytotoxic backbone alone, although no increase in response rate was shown. There are no data of randomized studies comparing the activity of a doublet of cytotoxics plus bevacizumab with a doublet plus cetuximab.

In the selection of the optimal treatment options for patients with metastatic CRC, the determination of the treatment goals and strategy are crucial. The possibility of resection of liver (or lung) metastases should be considered. In view of this and also because of the higher activity, multidrug combination regimens are proposed to many patients, although for a subgroup of patients with unresectable metastases without symptoms or risk of rapid deterioration and with comorbidity a sequential approach may be justified. In pa-

tients who are candidates for combination therapy determination of the KRAS status of the tumour can clearly determine the selection of the best combination regimen.

References

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