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REVIEW ARTICLE

Progress of transformational therapy in colorectal liver metastases

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Abstract

Colorectal cancer liver metastases (CLM) treatment is very important given the high incidence of colorectal cancer with liver metastases, which are primarily treated by surgical resection. Transformational therapy such as systemic chemotherapy, hepatic arterial infusion (HAI), portal vein embolization (PVE), ablation therapy, and targeted therapy, should be applied to CLM patients who are unable to undergo immediate surgery to improve patients' survival and quality of life.

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Cancer is a serious threat to human life and health and greatly influences socio-economic development. With the recent dramatic changes in disease patterns and demographic structure, ours is now an aging society and the incidence of cancer is increasing significantly as a consequence. Cancer is the most common and fourth most common cause of death in urban and rural areas of China [1–2], respectively. Morbidity and mortality due to colorectal cancer (CRC) are both considerably high, with CRC-related morbidity being the third most common cause of cancer-related morbidity and CRC-related mortality being the fourth most common cause of cancer-related mortality in China [3]. Worldwide, CRC ranks second in terms of cancer-related mortality [4]. There were 140,000 new cases of CRC in America in 2012 [5], and the CRC morbidity was the second among American female cancer patients in 2014 (9%) [6]. Because of effective prevention and treatment, the mortality rate due to CRC in America dropped significantly during the past few decades. The 1-year and 5-year survival rates were 83.2% and 64.3%, respectively; however, at the same time, the 5-year survival rate of CRC patients with metastasis plunged to only 11.7% [6].

The liver is the most common site of CRC metastasis. Twenty-five percent of CRC patients are diagnosed with liver metastases at the onset of early stage cancer, and another 30% of patients develop liver metastases during the disease progression course. CRC with liver metastases accounts for two-thirds of CRC deaths [4]. These facts suggest that effective treatment of CRC liver metastases (CLM) is important for improving survival and quality of life. Currently, radical surgical resection is still the gold standard in CLM surgical treatment; however, critical patients whose disease has progressed beyond indication for curative resection can benefit from a variety of combination treatments, particularly transformational therapy, to acquire the ability to undergo radical surgery and thus improve their survival [7].

Therefore, various transformational therapies should be actively applied to CLM patients in clinical practice. Treatments such as chemotherapy, interventional therapy, biological target therapy, and combination therapy can promote liver lesion shrinkage, decrease tumor stage, facilitate radical resection, decrease the recurrence rate, and increase 5-year survival.

Systemic chemotherapy

Surgical resection is the standard treatment for CLM [7], however, systemic chemotherapy is still the standard

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first-line treatment for patients who are unable to undergo an immediate operation. Transformational therapy can significantly decrease the size of metastatic lesions so that patients can become suitable for surgical resection [8–9] and thereby prolong survival time and lower the recurrence rate [10]. The ONG retrospective study in Singapore found that the survival rate of CLM patients approaches 30%–60% with preoperative chemotherapy, and thus half of the recurrence were limited to the liver, which persuasively demonstrates the effectiveness of preoperative chemotherapy [11].

Because of the serious side effects of chemotherapy, a combination of chemotherapy and targeted therapy is recommended in clinical practice to improve treatment efficiency and the R0 resection rate and to simultaneously reduce complications (specifically in regards to targeted therapy) [12–15]. In 2009, a retrospective analysis by an expert consensus recommended that, regardless of whether resection of liver metastases is feasible, most CLM patients should be treated with chemotherapy before surgery [16]. Poultsides et al. agree that chemotherapy should be the standard treatment in CLM patients without primary tumor obstruction or bleeding, and that prophylactic surgical resection of the primary tumor is not necessary [17]. However, another study supports the performance of surgical resection before chemotherapy [18] while another reports that the combination of chemotherapy and surgical resection of the primary tumor prolongs survival in CLM patients without symptoms or with no obvious symptoms [19]. Therefore, chemotherapy alone or combined with surgery both guarantee a long-term benefit to patients.

Hepatic arterial infusion (HAI)

In hepatic artery infusion (HAI), a pump is first connected to a catheter implanted in the liver and duodenum artery and the catheter tip then is guided into the junction of the duodenum liver-hepatic artery for delivery of chemotherapy drugs directly to the liver tissue. Since the metastatic liver lesions mainly derive nutrition from the hepatic artery, HAI therapy can not only reduce the cytotoxicity of chemotherapy drugs as compared to portal vein delivery to normal liver tissue, but also simultaneously increase the effective dose of local chemotherapy drugs in the liver lesions [20]. The overall effect is to effectively shrink the metastatic lesions while maximizing the protection of normal liver tissue [21]. Although the complication rate of HAI is approximately 20%, most affected patients are able to continue treatment after dose adjustment [22].

Portal vein embolization (PVE)

Portal vein embolization (PVE) is usually applied in the preoperative management of patients with marginal future liver remnants (FLRs) to increase their safety after surgical resection. In 1990, Makuuchi first proposed that preoperative PVE can induce liver atrophy in metastatic lesions and compensatory hypertrophy of the healthy liver parenchyma, thus preventing postoperative liver failure and enabling the resection of metastatic lesions in patients that, prior to PVE, could not tolerate surgery [23]. Anne also demonstrated the enhancement of liver regeneration in CLM patients after PVE, without an increase of surgical complications [24]. Liver regeneration reaches a steady state only after three weeks of PVE therapy [25]. However, PVE can promote the tumor growth rate in both embolic and non-embolic sites by increasing hepatic artery and portal vein-derived local growth factor levels [26–27]. It is possible to delay tumor growth after PVE with preoperative combination chemotherapy [27], but a recent study has rejected the use of such chemotherapy [28]. Therefore, imaging examination is necessary 3–6 weeks after PVE to evaluate the liver hyperplasia condition, in order to determine the possibility of new FLRs and radical resection of metastatic lesions or other therapeutic solutions [29].

Ablation

Ablation refers to the killing of tumor cells and surrounding normal cells by changing the local tissue temperature. Methods of ablation include radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation [30]. Ablation has many advantages, such as the retention of a larger area of hepatic parenchyma and a more convenient treatment procedure via percutaneous laparoscopic surgery. The goals of ablation are to enrich treatment selection of CLM patients and to reduce CLM incidence [30–31] as well as to significantly improve progression-free survival in CLM patients [32]. Therefore, despite its limitation of a maximum tumor size around the probe, ablation has been widely used for unresectable tumors or CLM lesions associated with serious complications [7, 33].

RFA is the most common ablation treatment in CLM patients [34]. It kills tumor cells and surrounding normal cells through high temperatures produced by electrodes that are implanted in the tumor under imaging guidance [30]. The median survival and 5-year overall survival of CLM patients treated with RFA are both lower than those of patients treated with resection, which is because of the multiple unresectable lesions in patients with advanced CLM treated with RFA and the presence of potentially

resectable occult metastases [35]. Research supports the use of RFA in advanced CLM patients, because it has many advantages such as a quick recovery, facilitates other transformational therapies, and avoids the risk of tumor progression [36].

In MWA, an electrode is implanted under ultrasound or CT guidance to produce microwaves to kill tumor cells. The advantages of MWA are the low rates of recurrence and complications [37]. MWA is more beneficial for lesions greater than 3 cm in size; however, the range of application is limited due to potentially huge incomplete ablation lesions and the heat back effect around large blood vessels [38].

In cryoablation, liquid nitrogen or argon gas is introduced into metastases under ultrasound guidance to eliminate tumor cells. Due to the high recurrence and complication rates [39–40], and possible fatal shock frozen (such as hypothermy, blood clotting abnormalities, respiratory failure, and renal failure) [41], cryoablation is rarely used nowadays.

Targeted therapy

The development of targeted drugs has improved the treatment effectiveness of metastatic CRC unprecedentedly. The combination of chemotherapy and targeted therapy can increase the overall survival of metastatic CRC patients to 30 months [42], and targeted therapy has been reported to greatly benefit CLM patients [43–47].

Cetuximab is a monoclonal antibody that inhibits the downstream epidermal growth factor signal transduction pathway [48]. Cunningham et al. demonstrated that the combination of cetuximab and chemotherapeutic regimens can improve the survival of CLM patients [49]; however, Cutsem suggested that cetuximab has no benefit in CLM patients with KRAS mutations, and thus, the efficiency of cetuximab depends on patients' KRAS status [50]. Studies in recent years revealed that cetuximab can significantly improve the overall recurrence rate, progression-free survival, and overall survival in KRAS wild-type patients if they are identified by KRAS testing before treatment [51]. Xu also discovered that, in comparison to chemotherapy alone, the combination of cetuximab and chemotherapy can improve the R0 resection rate, remission rate, and survival rate in KRAS wild type CLM patients, who were initially not able to undergo resection [‼HYPERLINK \l "_ENREF_46" \o "Ye, 2013 #2934" ¶46]. For patients with initially unresectable CLM, FOLFOX or FOLFIRI combined with cetuximab can shrink tumors significantly in preparation for resection [42]. To date, all of the studies support the important value of cetuximab in CLM patients in clinical practice, and there is no evidence of any obvious side effects, particularly of liver injury [15].

Bevacizumab

Bevacizumab is another common targeted drug in CRC treatment, mainly used to inhibit angiogenesis. The earlier bevacizumab is used, the greater is the benefit to CRC patients. Continuous administration of bevacizumab provides a greater benefit, and administration of bevacizumab to CLM patients can improve the tumor response rate and the R0 resection rate to some degree. Patients generally tolerate it well [44–45, 52]. However, consideration should be given to the regimen. The combination of chemotherapy and bevacizumab should be stopped 6 to 8 weeks before any surgical operation, otherwise it can lead to wound healing syndrome [53]. Xu also revealed that the three-drug regimen FOLFOXIRI can further improve treatment efficiency and the R0 resection rate and is a good option for CLM patients with KRAS mutations; however, physicians should be careful about the serious side effects of FOLFOXIRI in clinical practice.

Therefore, CLM patients should be treated with targeted drugs based on their individual condition to improve treatment efficiency, the resection rate, and the survival rate, and to reduce complications. In the end, adverse drug reactions should be supervised at all times during the treatment course in case of any fatal risk.

Conclusion

CLM patients suitable for surgical operation should be treated as soon as possible. Patients with potentially resectable metastases should be treated with appropriate transformational therapy methods to achieve tumor shrinkage and increase the possibility of resection as soon as possible. Since the resection rate is positively associated with treatment efficiency, the most suitable transformational therapy should be adopted, depending on each CLM patients' condition (e.g., chemotherapy plus cetuximab should be selected in cases of wild type KRAS and FOLFOXIRI plus bevacizumab should be selected in cases of mutated KRAS). If the patient's status is not available for consideration in treatment decision-making, first-line treatment should be initiated in advanced stage cases to improve the quality of life and prolong survival.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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