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REVIEW ARTICLE

What is the Optimal Cytotoxic Regimen for Advanced Colorectal Cancer?

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ABSTRACT

It is now well recognised that patients with metastatic colorectal cancer represent heterogeneous subgroups of patients with differing prognoses, because of differences in the number and sites of metastases, performance status, and the types of prior treatment. In fit patients with liver-only metastases in whom local ablative therapies may be rendered possible following downstaging of the metastases, multidrug systemic therapies achieving high tumour shrinkage rates may be the optimal choice. In contrast, patients with multiple sites of extrahepatic metastases or whose performance status is impaired, sequential single or two-drug regimens may be the more appropriate palliative approach, with the aim of extending progression-free survival. Recent studies have revealed that certain combinations of systemic therapies may result in overlapping toxicities or even worse clinical outcomes. A meta-analysis has also suggested that certain targeted therapies (monoclonal antibodies) may yield better clinical outcomes when combined with specific cytotoxic agents. Other special patient subgroups such as the elderly or those with impaired organ function deserve special consideration when selecting systemic therapies. This review summarises current data regarding optimal systemic therapy for different subgroups of patients with metastatic colorectal cancer.

Key Words: *Antineoplastic combined chemotherapy protocols; Colonic neoplasms; Liver neoplasms*

中文摘要

晚期大腸直腸癌的最佳細胞抑制劑治療是甚麼？

馬碧如

轉移性大腸直腸癌患者可以按著其轉移腫瘤的數量及位置、患者的日常體能狀態、及過往曾接受的治療，而分為不同組別，每個組別都有不同的預後。對於只有肝轉移癌的患者來說，因腫瘤縮小後可進行局部消融術，能大幅度提高腫瘤縮小率的多藥全身性治療可能是最佳療法。相反，如果病人有多個肝外轉移灶，或者其日常體能狀態受損，選擇順序單藥或雙藥制方案作為緩解治療可能更加適合，以增加其無惡化生存期。最近的研究結果顯示一些組合性的全身性治療可能會導致毒性重疊，或者引致更差的臨床結果。綜合分析亦發現當一些標靶療法（單克隆抗體） 結合特定的細胞抑制劑時，可能會有較佳的臨床療效。至於其他特殊的患者組別，例如年老的或者出現器官功能損壞的患者，當選擇全身性治療時，必需特別考慮。本文總結現今對於不同組別的大腸直腸癌患者的最佳全身性療法。

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in Hong Kong; over 20% of patients have metastatic disease at diagnosis.[1] It is now recognised that patients with metastatic CRC represent a biologically heterogeneous group, for whom the prognosis is strongly influenced by a number of factors including the patient's performance status and the number of sites of metastases. This insight is reflected in the latest edition of the American Joint Committee on Cancer (TNM) staging criteria, in which stage IV CRC has been subdivided into stages IVa and IVb.[2] Patients with the former have oligometastases involving only one site or organ, while those with the latter have metastases at multiple sites or organs. The prognosis and therapeutic goals for patients with stage IVa CRC are quite different from those with stage IVb disease. For stage IVa disease, the aim is to optimise the chance of local resection / ablation of oligometastases by adopting a more intensive, multidrug cytotoxic regimen with a high rate of tumour response. In contrast, when the chance of achieving surgical cure is negligible such as among patients with stage IVb CRC, the goal is to slow the rate of cancer progression and minimise treatment-related toxicities. Thus, the definition of an 'optimal' cytotoxic regimen for metastatic CRC depends on the clinical context and therapeutic intent. In this review, the optimal application of cytotoxic chemotherapy for metastatic CRC is discussed in three sections: (a) the development of optimal drug combination and sequencing; (b) optimising the systemic treatment of patients with stage IVa metastatic CRC, and (c) optimising the systemic treatment in stage IVb metastatic CRC.

DRUG COMBINATIONS AND SEQUENCES

The Development of Cytotoxic Drug Combinations in Contemporary Practice

For decades, 5-fluorouracil (5FU) was the only available agent with consistent activity in metastatic CRC and as a result, oncologists have learnt how to optimise its use in clinical practice. Intravenous (IV) 5FU when administered as a continuous infusion has comparatively less gastrointestinal and marrow toxicity than when given as bolus,[3] and the use of concomitant leucovorin (LV) has improved its biological activity.[4] Similarly, phase III studies comparing bolus 5FU and oral fluoropyrimidines (such as capecitabine) in metastatic CRC have confirmed similarities in clinical efficacy but with differences in toxicity. Oral 5FU generally has a lower liability to give rise to mucositis, diarrhoea, emesis and myelosuppression, but a higher liability to cause hand-foot syndrome.[5]

When irinotecan and oxaliplatin became available in the late 1990s, two-drug regimens consisting of a 'backbone' of fluoropyrimidine were developed, partly based on some evidence of drug synergism in preclinical models of CRC (involving 5FU and oxaliplatin or irinotecan).[6,7] Examples of such regimens which are now popular include the FOLFOX and FOLFIRI regimens. These regimens were built upon the 'De Gramont' regimen, which entailed a backbone consisting of 48-hour infusions of 5FU at 2-weekly intervals, with or without a preceding 5FU 'loading' dose bolus. This regimen exploited the unique properties of 5FU as an S-phase–specific anti-metabolite with a short half-life, so that prolonged relatively lower dose-range 5FU infusions might result in better killing of cancer cells, and less marrow and gastrointestinal tract toxicity than bolus administration of higher doses.[8] Among successive generations of FOLFOX regimens developed to date, FOLFOX-4[9] and FOLFOX-6[10] regimens are the most commonly used. Randomised studies of FOLFOX-4 and FOLFOX-6 have confirmed their efficacy and tolerability in the first-line treatment of metastatic CRC, where the overall response rate is expected to be between 45% and 55%, with a frequency of grade 3-4 neuropathy of 18% and neutropenia between 44% and 50%.[11,12] For the FOLFIRI regimen, the overall response rate is generally around 38% to 54% in the first-line setting, with a grade 3-4 diarrhoea frequency of around 10% and neutropenia of around 24%.[11,13]

As infusional 5FU mandates the use of central venous delivery systems, oral 5FU derivatives such as capecitabine has become a more convenient therapeutic alternative. Randomised studies such as the 'TREE' and the NO16966 compared the use of oxaliplatin and capecitabine (XELOX or CAPOX) with the FOLFOX regimen in the first-line treatment of metastatic CRC, and found no significant differences in overall and progression-free survival.[14,15] However, the XELOX or CAPOX regimens are associated with a higher frequency of grade 3-4 diarrhoea and hand-foot-syndrome, while FOLFOX has a higher risk of causing grade 3-4 neutropenia.[16] In comparison, the development of irinotecan-capecitabine combinations

(such as the XELIRI and CAPIRI regimens) has been hampered by problems with overlapping gastrointestinal toxicities. A phase I study which evaluated a three-weekly XELIRI regimen reported the maximum tolerated dose of irinotecan and capecitabine to be 250 mg/m^2 and 1000 mg/m^2 twice a day, respectively. In another study, capecitabine did not seem to significantly affect the pharmacokinetics of irinotecan.[17] The three-weekly XELIRI or CAPIRI schedule is generally associated with a 20 to 25% of grade 3-4 diarrhoea in phase II studies in CRC.[18,19] FOLFIRI and the three-weekly CAPIRI regimens were compared in the phase III BICC study, where patients were randomised to either FOLFIRI, CAPIRI, or the now obsolete modified IFL regimen with added bevacizumab.[20] The CAPIRI arm was terminated following a protocol amendment, because of concerns over toxicity giving rise to grade 3 to 4 rate of diarrhoea, neutropenia and nausea reported as 48%, 32% ,and 18%, respectively.[20] A subsequent study attempted to reduce the toxicity of the XELIRI regimen by adopting a lower dose of irinotecan (<180 mg/m^2) and at a two-weekly schedule, and found an overall response rate of 32% and a median overall survival of up to 19 months, which is comparable to the three-weekly regimen reported in the BICC study.[20,21]

Given the higher response rates associated with multidrug cytotoxic regimens in CRC, some researchers have evaluated the efficacy and tolerability of using all three key cytotoxic agents in the first-line setting, namely, oxaliplatin, irinotecan, and 5FU. The FOLFOXIRI regimen (irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, LV 200 mg/m^2, 5FU 3200 mg/m^2 at a 48-hour continuous infusion) was compared with FOLFIRI in a phase III study of metastatic CRC in the first-line setting.[22] FOLFOXIRI was superior to FOLFIRI in terms of response and overall survival, albeit with higher rates of grade 3 to 4 diarrhoea and febrile neutropenia (which did not reach statistical significance). Interestingly, the magnitude of benefit reported with FOLFOXIRI compared favourably with that reported with cetuximab-FOLFIRI in patients with *KRAS*-wild-type CRC in the CRYSTAL study.[13] For instance, FOLFOXIRI is associated with an overall response rate of 66% with a hazard ratio of 0.63 for progression-free survival and 0.70 for overall survival, while cetuximab-FOLFIRI is associated with a response rate of 59.3% with a hazard ratio of 0.68 for progression-free survival and 0.84 for overall survival.[13]

Lessons Learnt from Clinical Studies on Drug Sequencing in Metastatic Colorectal Cancer

In a pooled analysis of seven phase III studies in metastatic CRC, patients who were exposed to all three key cytotoxic agents (5FU, oxaliplatin, and irinotecan) during the course of their illness had significantly longer survival than those who did not.[23] However, this analysis did not address questions pertaining to the optimal sequence of drug administration. The randomised studies by the French GERCOR group and the Dutch CAIRO study were both designed to address this question.[11,24] In the French study, the use of either first-line FOLFOX followed by FOLFIRI (or the reverse sequence) did not differ significantly in terms of overall survival or response rates. The main differences between the two sequences were toxicities and also a better response rate and progression-free survival associated with FOLFOX6 use in the second-line setting.[11] In the Dutch study, no statistically significant differences in overall survival and toxicity were found between patients who were randomised to sequential monotherapies versus a combinatorial strategy.[24] The finding reported in the CAIRO study is supported by the result of the recently published FOCUS study, which reported no statistically significant difference in overall survival (the study's primary endpoint) between patients randomised to a sequential arm of monotherapies, or to two-drug combination regimens.[25] In the FOCUS and CAIRO studies, the key advantages of using drug combinations upfront appeared to be better response rate and progression-free survival.[25]

Are There Any 'Preferred' or Even 'Bad' Drug Partnerships?

The result of a meta-analysis by Golfinopoulos et al[26] generated an intriguing hypothesis that for metastatic CRC, some drug partnerships may be more effective than others. This also raised the possibility of some negative interactions between certain cytotoxic agents and monoclonal antibodies. However, this meta-analysis was published before the publication of some of the major phase III studies involving combinations of chemotherapy and cetuximab, such as the CRYSTAL and COIN studies and so its conclusion may not be applicable to anti-epidermal growth factor receptor (EGFR) antibodies.[13,15,27] This meta-analysis found that the margin of benefit in overall survival (in terms of hazard ratios) seemed to be larger when bevacizumab was combined with irinotecan than with oxaliplatin.[26] The recent publication of the COIN study also adds

to this hypothesis of negative interactions between certain drugs, such as capecitabine and cetuximab.[28] In this large phase III study of 1630 patients with previously untreated metastatic CRC, cetuximab modestly improved the response rate and overall survival in a subgroup of patients with only one site of metastasis and had received concomitant oxaliplatin and 5FU. The lack of survival benefit in patients who received capecitabine-based combinations was attributed to the higher frequency of overlapping skin and gastrointestinal toxicities with cetuximab and capecitabine, resulting in reduced dose intensity in the capecitabine-treated arm. The possibility of a negative interaction between oxaliplatin and cetuximab was also raised.[28] The result of the COIN study was unexpected because two other smaller randomised studies by a German and a Swiss group found that the addition of cetuximab to capecitabine-based regimens (CAPOX / XELOX or CAPIRI) in the first-line treatment of metastatic CRC did not significantly increase grade 3 to 4 toxicities.[29,30] Interestingly, the median overall survival in these two studies for the CAPOX-cetuximab or XELOX-cetuximab arm (20.5 to 23.5 months) were better than the cetuximab-XELOX arm (17.1 months) in the COIN study, suggesting that factors other than negative drug interactions may have contributed to the negative result in the COIN study. These include institutional / regional differences in the standard of supportive care, the number of lines of chemotherapy delivered, the availability of bevacizumab, and the patients recruited.[28]

Some drug combinations not only undermine the margin of benefit of specific drugs, they may even have detrimental effects on survival. The combinations of bevacizumab and anti-EGFR antibodies such as cetuximab and panitumumab have been shown to reduce progression-free and / or overall survival in phase III studies.[31,32] Notably, more frequent toxicities were reported in patients who received both antibodies, raising the question of negative interactions between different antibodies and cytotoxic regimens.

OPTIMAL CYTOTOXIC REGIMEN FOR STAGE IVA METASTATIC COLORECTAL CANCER

The multimodal approach to the treatment of isolated liver metastases in CRC has enabled some patients to achieve long-term remissions, and multidrug cytotoxic regimens with high response rates can facilitate local ablative therapies for liver metastases. This approach is supported by a pooled analysis on studies of neoadjuvant chemotherapy for liver metastases in CRC, which found a strong correlation between response rates to chemotherapy and the subsequent rates of liver resection.[33] In the literature, the response rates to three- or four-drug regimens were generally higher than for two-drug regimens in metastatic CRC, and also among selected populations with liver-only metastases (i.e. stage IVa). For three-drug regimens containing only cytotoxic agents, the objective response rate has been reported to be around 58% for FOLFOXIRI in unselected populations, and as high as 70% for FOLFIRINOX[34] in patients with unresectable liver-only metastases.[22,23] The common experience with these regimens included a high rate of grade 3 to 4 neutropenia (50-63%), diarrhoea (20-30%), and fatigue (up to 20%).[22,23] These response rates were not inferior to those reported with three-drug regimens that contained antibodies such as bevacizumab and cetuximab. For *KRAS*-wild type patients, the combination of cetuximab with two-drug regimens such as FOLFOX or FOLFIRI has been shown to yield response rates of 70% in the CELIM study, which included patients with unresectable liver metastases.[33] In the BOXER study, combination of bevacizumab and CAPOX may yield response rates of up to 78% in patients with unresectable liver metastases.[35] In these studies, such antibody-based regimens did not appear to significantly increase perioperative mortality and morbidity.[35,36] However, the number of cycles of chemotherapy was found to be prognostically significant in a retrospective study from the M.D. Anderson Cancer Center, where the administration of nine or more than nine cycles of chemotherapy was associated with a higher risk of postoperative hepatic insufficiency.[37]

OPTIMAL CYTOTOXIC REGIMEN FOR STAGE IVB METASTATIC COLORECTAL CANCER

For patients with metastases at multiple sites or impaired performance status in whom the main aim of treatment is to slow down cancer progression, one should administer drugs or drug sequence / schedules that can best stabilise the disease without excessive overlapping toxicities. One of the approaches that has been evaluated in the randomised setting has been the use of sequential monotherapies in first- or second-line treatment and reserving drug combinations for progression. This approach was tested in the CAIRO and FOCUS studies as discussed above.[24,25] Other approaches included the use of reduced starting doses

of chemotherapy, or single-agent capecitabine as opposed to a combination or IV 5FU-based regimen. These are preferred for patients in whom full-dose IV chemotherapy is considered not feasible, such as the elderly or those with impaired performance status. These alternative approaches were evaluated in the FOCUS2 study, where 459 patients were randomised to first-line monotherapies with capecitabine or 5FU/LV, or an oxaliplatin-based two-drug regimen at an 80% starting dose. This study found that although the addition of oxaliplatin did not significantly increase grade 3 to 4 toxicity, only a non-significant trend towards better progression-free survival was noted. In contrast, replacement of 5FU/LV with capecitabine did not improve the quality of life of such patients.[38] Non-cytotoxic approaches such as cetuximab (or where available, panitumumab) alone are also effective palliative treatments in patients who are deemed not fit for multi-agent chemotherapy and have *KRAS* wild-type tumours.[39,40] Collectively, the current data suggest that the palliative benefits of cytotoxic agents in metastatic CRC are not negated by adopting a lower starting dose of chemotherapy during the first few treatment cycles, or by using single agents in sequence.

CONCLUSION

The optimal cytotoxic regimen for metastatic CRC should be tailored according to the therapeutic intent for different patient subgroups. If the intent is palliation, then existing data suggest that the first-line use of single agents in sequence, or use of lower starting doses of chemotherapy are acceptable alternatives to multidrug combinations especially in the elderly or patients with impaired performance status.[41] If maximum tumour shrinkage is desired in order to optimise the chance for potentially curative resection of liver metastases, then existing literature suggests the use of multidrug combinations with or without a monoclonal antibody, depending on the *KRAS* mutation status and medical fitness of the patient. Certain drug partnerships may have negative interactions, such as combining two antibodies with chemotherapy, and are contraindicated. Other combinations such as capecitabine and cetuximab should be used with caution and are best avoided in patients who cannot tolerate overlapping gastrointestinal toxicities and thus require dosage reductions.

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REFERENCES

1. Law CK, Mang O. Cancer incidence in Hong Kong. Medical Bulletin. 2007;12:18-21.
2. Edge SG, Byrd D, Compton CC, et al, editors. Colon and rectum. 7th edition. New York: Springer; 2010.
3. Rich TA, Shepard RC, Mosley ST. Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. J Clin Oncol. 2004;22:2214-32.
4. Petrelli N, Douglass HO Jr, Herrera L, Russell D, Stablein DM, Bruckner HW, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. Gastrointestinal Tumor Study Group. J Clin Oncol. 1989;7:1419-26.
5. Twelves C; Xeloda Colorectal Cancer Group. Capecitabine as first-line treatment in colorectal cancer. Pooled data from two large, phase III trials. Eur J Cancer 2002;38(Suppl 2):15-20.
6. Raymond E, Buquet-Fagot C, Djelloul S, Mester J, Cvitkovic E, Allain P, et al. Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. Anticancer Drugs. 1997;8:876-85.
7. Azrak RG, Cao S, Slocum HK, Tóth K, Durrani FA, Yin MB, et al. Therapeutic synergy between irinotecan and 5-fluorouracil against human tumor xenografts. Clin Cancer Res. 2004;10:1121-9.
8. Raftery L, Goldberg RM. Optimal delivery of cytotoxic chemotherapy for colon cancer. Cancer J. 2010;16:214-9.
9. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18:2938-47.
10. Maindrault-Goebel F, Louvet C, André T, Carola E, Lotz JP, Molitor JL, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. Eur J Cancer. 1999;35:1338-42.
11. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22:229-37.
12. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22:23-30.
13. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360:1408-17.
14. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol. 2008;26:3523-9.
15. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008;26:2006-12.
16. Schmoll HJ, Arnold D. Update on capecitabine in colorectal cancer. Oncologist. 2006;11:1003-9.
17. Czejka M, Schueller J, Hauer K, Ostermann E. Pharmacokinetics and metabolism of irinotecan combined with capecitabine in patients with advanced colorectal cancer. Anticancer Res.

2005;25:2985-90.
18. Patt YZ, Lee FC, Liebmann JE, Diamandidis D, Eckhardt SG, Javle M, et al. Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. Am J Clin Oncol. 2007;30:350-7.
19. Kim TW, Kang WK, Chang HM, Park JO, Ryoo BY, Ahn JS, et al. Multicenter phase II study of oral capecitabine plus irinotecan as first-line chemotherapy in advanced colorectal cancer: a Korean Cancer Study Group trial. Acta Oncol. 2005;44:230-5.
20. Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol. 2007;25:4779-86.
21. Garcia-Alfonso P, Muñoz-Martin A, Mendez-Ureña M, Quiben-Pereira R, Gonzalez-Flores E, Perez-Manga G. Capecitabine in combination with irinotecan (XELIRI), administered as a 2-weekly schedule, as first-line chemotherapy for patients with metastatic colorectal cancer: a phase II study of the Spanish GOTI group. Br J Cancer. 2009;101:1039-43.
22. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25:1670-6.
23. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol. 2004;22:1209-14.
24. Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet. 2007;370:135-42.
25. Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. Lancet. 2007;370:143-52.
26. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. Lancet Oncol. 2007;8:898-911.
27. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet. 2011;377:2103-14.
28. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet. 2010;377:2103-14.
29. Borner M, Koeberle D, Von Moos R, Saletti P, Rauch D, Hess V, et al. Adding cetuximab to capecitabine plus oxaliplatin (XELOX) in first-line treatment of metastatic colorectal cancer: a randomized phase II trial of the Swiss Group for Clinical Cancer Research SAKK. Ann Oncol. 2008;19:1288-92.
30. Moosmann N, von Weikersthal LF, Vehling-Kaiser U, Stauch M, Hass HG, Dietzfelbinger H, et al. Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first-line treatment for patients with metastatic colorectal cancer: AIO KRK-0104—a randomized trial of the German AIO CRC study group. J Clin Oncol. 2011;29:1050-8.
31. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009;27:672-80.
32. Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563-72.
33. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010;11:38-47.
34. Ychou M, Viret F, Kramar A, Desseigne F, Mitry E, Guimbaud R, et al. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases. Cancer Chemother Pharmacol. 2008;62:195-201.
35. Wong R, Cunningham D, Barbachano Y, Saffery C, Valle J, Hickish T, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. Ann Oncol. 2011;22:2042-8.
36. Folprecht G, Schuette K, Stoehlmacher J, Goekkurt E, Trarbach T. Cetuximab and FOLFOXIRI: Dose-escalation study in previously untreated patients with metastatic colorectal cancer. Proceedings of the 2010 Gastrointestinal Cancers Symposium. 2010 January 22-24; Chicago: American Society of Clinical Oncology GI; Abstract 480.
37. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2010;17:2870-6.
38. Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd SF, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet. 2011;377:1749-59.
39. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357:2040-8.
40. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25:1658-64.
41. Hewish M, Cunningham D. First-line treatment of advanced colorectal cancer. Lancet. 2011;377:2060-2.