

Advances in Chemotherapy against Advanced or Metastatic Colorectal Cancer

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Key Words

Colorectal cancer · Chemotherapy · 5-Fluorouracil · Leucovorin · Oxaliplatin · Irinotecan · Molecular targeting

Abstract

In the early 1990s, some prospective controlled trials revealed the superiority of chemotherapy for survival compared with best supportive care for advanced or metastatic colorectal carcinoma. Until recently, 5-fluorouracil (5-FU) and leucovorin (LV) were the standard therapies against advanced or metastatic colorectal cancer. Theoretically, LV should increase the antitumor activity of 5-FU, although this effect of LV addition has been controversial. A meta-analysis which analyzed 21 randomized controlled trials revealed that a combination of 5-FU and LV doubled the response rate compared with 5-FU alone (from 11 to 21%) and prolonged the median survival time by about 1 month (from 10.5 to 11.7 months). Chemotherapy against advanced or metastatic colorectal cancer has steadily advanced after the introduction of triplet regimens containing 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (CPT-11) and (trans-R,R-1,2-diamine cyclohexane)oxalatoplatinum(II) (L-OHP). For LV/5-FU/CPT-11, the regimen in which 5-FU is administered with continuous infusion (FOLFIRI) is preferred compared with the 5-FU bolus infusion. According to the results of the randomized controlled trial comparing FOLFIRI followed by FOLFOX6 and the reverse sequence, FOLFOX6 followed by FOLFIRI, in the treatment of advanced colorectal cancer, FOLFIRI and FOLFOX are now considered to have al-

most the same efficacy in the treatment of advanced or metastatic colorectal cancer. FOLFIRI followed by FOLFOX or FOLFOX followed by FOLFIRI provide a median survival time of about 21 months in advanced or metastatic colorectal cancer. Both an anti-vascular endothelial growth factor monoclonal antibody, bevacizumab, and an anti-epidermal growth factor receptor monoclonal antibody, cetuximab, should prolong the survival of advanced or metastatic colorectal cancer by 2–3 months in combination with FOLFIRI or FOLFOX. However, from the viewpoint of medical economics, because of the high acquisition costs in relation to clinical benefits, antibodies are unlikely to represent a cost-utility solution. New agents, including macromolecule agents, small-molecule agents and vaccines, will be introduced alongside chemotherapy against colorectal cancer. Subsequently, clinical researchers will have to consider the cost-utility of these agents.

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Introduction

Colorectal cancer is the third leading cause of cancer death in Japan. Approximately 40% of all patients develop metastatic disease. Consequently, chemotherapy which provides obvious prolongation of survival in metastatic colorectal cancer is quite useful. Until recently, 5-FU, which has been available for over 40 years, and folinate calcium [leucovorin (LV)] have been the standard therapy. However, LV/5-FU showed no major impact on

survival. Chemotherapy against advanced or metastatic colorectal cancer has steadily improved with the introduction of triplet regimens containing irinotecan [7-ethyl-10-(4-[1-piperidino]-1-piperidino)carbonyloxy-camptothecin (CPT-11)] or oxaliplatin [(trans-R,R-1,2-diamine cyclohexane)oxalatoplatinum(II) (L-OHP)]. Chemotherapy for advanced or metastatic colorectal cancer has been supplemented with other promising agents: monoclonal antibodies against vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). This review describes progress in chemotherapy against advanced or metastatic colorectal cancer over the last 2 decades.

Rationale of Chemotherapy against Advanced or Metastatic Colorectal Cancer

Until the 1980s, the effect of chemotherapy on advanced or metastatic colorectal cancer was unclear. Some prospective controlled trials were performed to estimate the survival benefit of chemotherapy in patients with advanced, recurrent or metastatic colorectal cancer. Scheithauer et al. [1] reported the results of a prospective randomized trial which compared the survival and quality of life in patients given combination chemotherapy and best supportive care (BSC) and in patients given only BSC. The chemotherapy consisted of 5-FU, folinic acid and cisplatin. Forty previously untreated patients with locally recurrent or metastatic colorectal cancer were enrolled. The patients were randomized to receive chemotherapy and BSC or only BSC at a ratio of 2:1. Chemotherapy consisted of 5-FU, LV and cisplatin. Overall survival (OS) was significantly longer for patients given chemotherapy and BSC (11.0 months) than for those receiving only BSC (5.0 months, $p = 0.006$). Mild to moderate gastrointestinal toxicity was commonly observed in the chemotherapy group. However, there was no significant difference in the quality of life scores between the 2 groups. According to the results of this study, chemotherapy against advanced or metastatic colorectal cancer was considered to prolong survival without reducing quality of life.

5-FU and LV

LV is a reduced folate which is easily metabolized to methylenetetrahydrofolate ($\text{CH}_2\text{H}_4\text{PteGlu}$). $\text{CH}_2\text{H}_4\text{PteGlu}$ is an essential cofactor in the inhibition of thymidylate

synthase (TS, EC 2.1.1.45) by 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), which is an active form of 5-FU [2]. TS catalyzes the reductive methylation of deoxyuridine monophosphate to form deoxythymidine monophosphate, which is the rate-limiting reaction in de novo synthesis of pyrimidine nucleotides. $\text{CH}_2\text{H}_4\text{PteGlu}$ is a cofactor in this reaction to provide the 1-carbon unit, CH_2 . FdUMP binds to the active site of TS with higher affinity than dUMP, which is the native substrate of TS [3]. However, FdUMP is not methylated due to binding of fluoride to the 5th position of uracil, where hydrogen is substituted by the 1-carbon unit CH_3 with the catalysis of TS. Then, FdUMP and $\text{CH}_2\text{H}_4\text{PteGlu}$ bind tightly and occupy the active site of TS. Thus, an inactive ternary complex is formed with TS, FdUMP and $\text{CH}_2\text{H}_4\text{PteGlu}$, and TS is competitively inhibited. As the amount of reduced folates, including $\text{CH}_2\text{H}_4\text{PteGlu}$, is limited, TS inhibition by FdUMP is insufficient due to lack of $\text{CH}_2\text{H}_4\text{PteGlu}$. Other reduced folates such as $\text{CH}_3\text{H}_4\text{PteGlu}$, $\text{CHH}_4\text{PteGlu}$ and $\text{CHOH}_4\text{PteGlu}$ play essential roles to transfer the 1-carbon unit in important reactions to maintain homeostasis and to synthesize nucleotides. Consequently, simultaneous use of reduced folate and LV should increase the antitumor activity of 5-FU.

Many studies revealed that the combination of LV and 5-FU (LV/5-FU) increased the response rate (RR) of advanced, recurrent or metastatic colorectal cancer compared with 5-FU alone. However, the effect of LV addition is controversial because the RR of LV/5-FU were 20–30%, and the chemotherapy barely affected the median survival time (MST). A meta-analysis which analyzed 21 randomized controlled trials (RCTs) revealed that the combination of 5-FU and LV increased the RR 2-fold compared with 5-FU alone (from 11 to 21%) and prolonged the MST by 1 month (from 10.5 to 11.7 months) [4].

Several regimens have been developed for LV/5-FU. The differences between these regimens are mainly the method of administration of 5-FU, bolus or infusion. Madajewicz et al. [5] reported weekly administration of LV/5-FU with bolus 5-FU. Their regimen is now called the Roswell Park Memorial Institute regimen. In the USA, another LV/5-FU regimen, in which LV and 5-FU are administered for 5 consecutive days for 4 weeks, was also developed [6]. The latter regimen is called the Mayo regimen. The Roswell Park Memorial Institute and Mayo regimens are comparable in terms of clinical effect, but the Mayo regimen is considered more toxic. On the other hand, LV/5-FU regimens, in which continuous infusion

of 5-FU was applied, were developed in Europe. De Gramont et al. [7] reported a unique regimen for LV/5-FU, in which LV 200 mg/m² was administered with a 2-hour infusion followed by a 5-FU 400 mg/m² bolus and 22-hour continuous 5-FU 600 mg/m² infusion, repeated on days 1 and day 2 for 2 weeks. They named this regimen LV5FU2. Recently, a simplified LV5FU2 regimen (sLV5FU2) has been introduced. LV infusion and bolus 5-FU are performed only on day 1, followed by 46-hour continuous infusion of 5-FU in sLV5FU2.

Another LV/5-FU regimen, in which 5-FU is administered with continuous infusion, was introduced by the Association of Medical Oncology of the German Cancer Society (AIO) [8]. In the AIO regimen, LV 500 mg/m² was administered with 2-hour infusion followed by 24-hour continuous infusion of 5-FU 2,600 mg/m² weekly for 6 weeks during 8 weeks. It was unclear which was better for prolongation of survival, bolus 5-FU or infusional 5-FU, in LV/5-FU against advanced or metastatic colorectal cancer.

The clinical effect of chemotherapy against colorectal cancer has made rapid progress strides with the development of the combination regimens, LV/5-FU/CPT-11 and LV/5-FU/L-OHP, described below. In these triplet regimens, especially for LV/5-FU/CPT-11, infusional 5-FU demonstrated a better outcome than bolus 5-FU [9].

CPT-11 and LV/5-FU/CPT-11 against Recurrent or Metastatic Colorectal Cancer

Camptothecin is a plant alkaloid-derived antitumor agent. CPT was purified from extraction of *Camptotheca acuminata*. CPT-11 is a water-soluble analogue of CPT, which showed a higher antitumor activity and less toxicity than CPT [10]. Topoisomerase I, which is the target enzyme of CPT-11, regulates the superhelical density of DNA by transiently nicking 1 strand of the DNA helix. Topoisomerase I may be involved in many aspects of DNA metabolism, including transcription, replication and recombination. Consequently, inhibition of topoisomerase I causes DNA breakage and sequential cell death [11]. Although CPT-11 alone has considerable antitumor activity against colorectal cancer, it showed a marked combination effect with LV/5-FU.

Saltz et al. [12] reported the results of a comparison of LV/5-FU/CPT-11, LV/5-FU and CPT-11 alone as first-line chemotherapy for metastatic colorectal cancer. A total of 683 patients were randomized to the LV/5-FU/CPT-11 group (LV 20 mg/m² bolus, 5-FU 500 mg/m² bolus and

CPT-11 125 mg/m² infusion weekly for 4 weeks during 6 weeks; n = 231), the LV/5-FU group (LV 20 mg/m² bolus, 5-FU 425 mg/m² bolus daily for 5 consecutive days for 4 weeks; n = 226) and the CPT-11 group (CPT-11 125 mg/m² infusion weekly for 4 weeks during 6 weeks; n = 226). As compared with the LV/5-FU group, the LV/5-FU/CPT-11 group showed a significantly higher RR (39 vs. 21%; $p < 0.001$) and a longer MST (14.8 vs. 12.6 months; $p = 0.04$). The results for the CPT-11 group were similar to those for the LV/5-FU group. The schedule of LV/5-FU/CPT-11 used in this study is called the Saltz regimen or IFL (fig. 1). Although the efficacy of IFL was sensational at that time, this regimen was too toxic. The mortality rate within 60 days from the start of IFL was 6.7%.

Infusional 5-FU and LV combined with CPT-11 is called FOLFIRI. The first report of FOLFIRI was sLV5FU2 with CPT-11 (fig. 1) [13]. FOLFIRI was introduced as a third-line chemotherapy for metastatic colorectal cancer. Among 33 patients who underwent FOLFIRI, 2 had partial responses and the RR was 6%. Twenty patients (61%) had stable disease and the disease control rate was 67%. From the start of FOLFIRI, the median progression-free survival (PFS) was 18 weeks and the MST was 43 weeks. National Cancer Institute Common Toxicity Criteria (NCI-CTC) toxicities grade 3–4 were nausea (15%), diarrhea (12%) and neutropenia (15%). Overall, 10 patients (30%) experienced grade 3–4 toxicity.

FOLFIRI is now recognized as one of the first-line chemotherapy regimens for recurrent or metastatic colorectal cancer, it has almost the same efficacy as LV/5-FU/L-OHP described in detail below.

L-OHP and LV/5-FU/L-OHP against Recurrent or Metastatic Colorectal Cancer

L-OHP has potential against many cancer cell lines and tumors, including some that are primarily resistant to cisplatin and carboplatin [14]. The 1,2-diaminocyclohexane (DACH) ligand provides higher lipophilicity compared to cis- and carboplatin, which is expressed by a large volume of distribution and a slower excretion through the kidneys. The lipophilic properties of oxaliplatin can also contribute to differences in general toxicity, as well as to an altered cellular uptake [15].

The DACH ligand plays a crucial role in the cytotoxic profile of oxaliplatin, forming intra- or interstrand adducts in the ultimate target DNA. The adducts are recognized and processed differently from those of cisplatin and carboplatin. Furthermore, due to the methylene

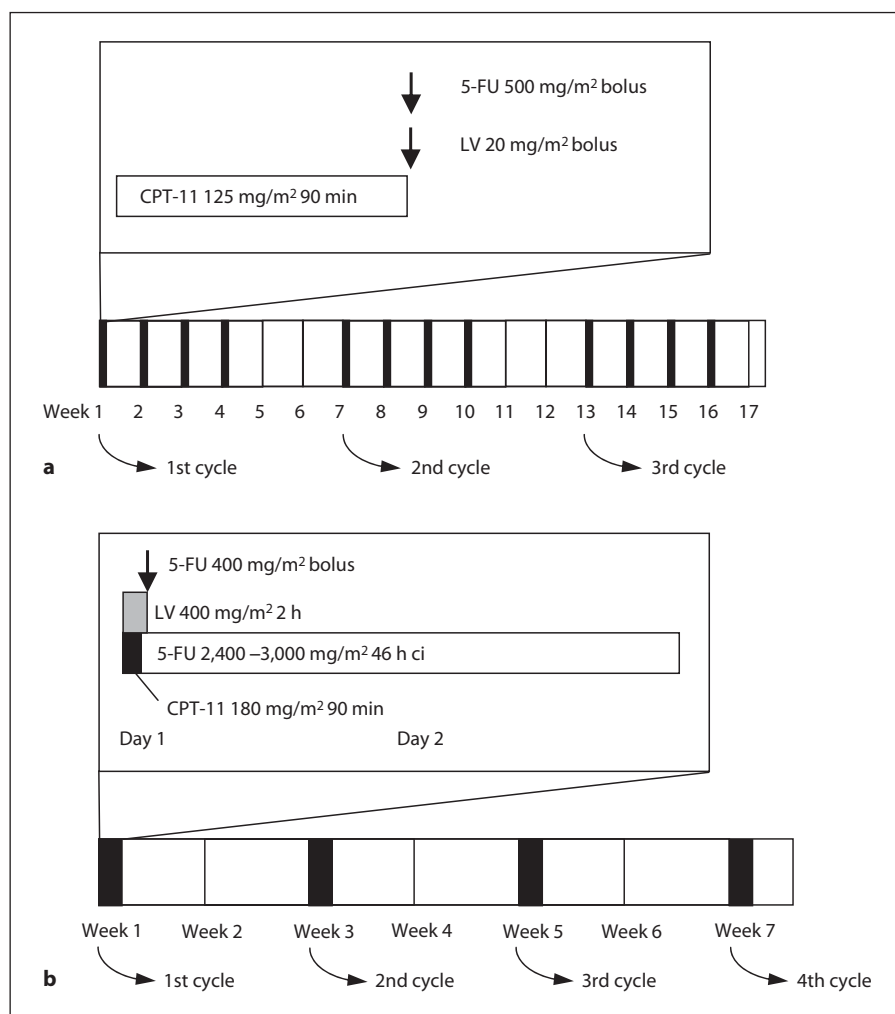


Fig. 1. Drug administration schemata of IFL (a) and FOLFIRI (b). ci = Continuous infusion.

units of the cyclohexane ring, an unpolar region is formed at the DNA. Both features contribute to the different recognition and repair of adducts formed between oxaliplatin and the DNA [15].

The platinum complexes with the amino groups in the *trans* position display better cytotoxic and anticancer activities than the *cis*-(*R,S*) isomer. Furthermore, the *trans*-(*R,R*) isomer shows significantly more potent antitumor activity than the *trans*-*S,S* congener. The DACH ligand provides such a marked influence on the pharmacological profile and effectiveness of oxaliplatin in primarily *cis*- and carboplatin-resistant tumors that derivatization at the *trans*-*R,R*-cyclohexane-1,2-diamine moiety could lead to improved anticancer properties [15]. L-OHP alone showed an insufficient clinical effect on recurrent or metastatic colorectal cancer. However, it is widely known that L-OHP has a synergistic effect when it is used with 5-FU/

LV. L-OHP has unique adverse effects, including sensory neuropathy, lack of coordination due to peripheral nerve disturbances and allergy.

De Gramont et al. [16] first reported the efficacy of LV/5-FU/L-OHP and named their regimen FOLFOX. Originally, FOLFOX consisted of LV 200 mg/m² 2-hour infusion, followed by 5-FU 300 mg/m² bolus and 300 mg/m² 22-hour infusion both on days 1 and 2 for 2 weeks. Then, in the absence of toxicity, 5-FU was increased to a 400-mg/m² bolus and 22-hour infusion in course 2 and to 500 mg/m² in course 3 and from course 4 maintained at 500 mg/m². In the first phase II study, 37 patients with advanced measurable colorectal cancer received the original FOLFOX. One patient (2.7%) had a complete response, 19 (51.4%) had partial responses, and the RR was 54%. The MST was 18 months and 21% of the patients were alive at 2 years. After that, several FOLFOX regi-

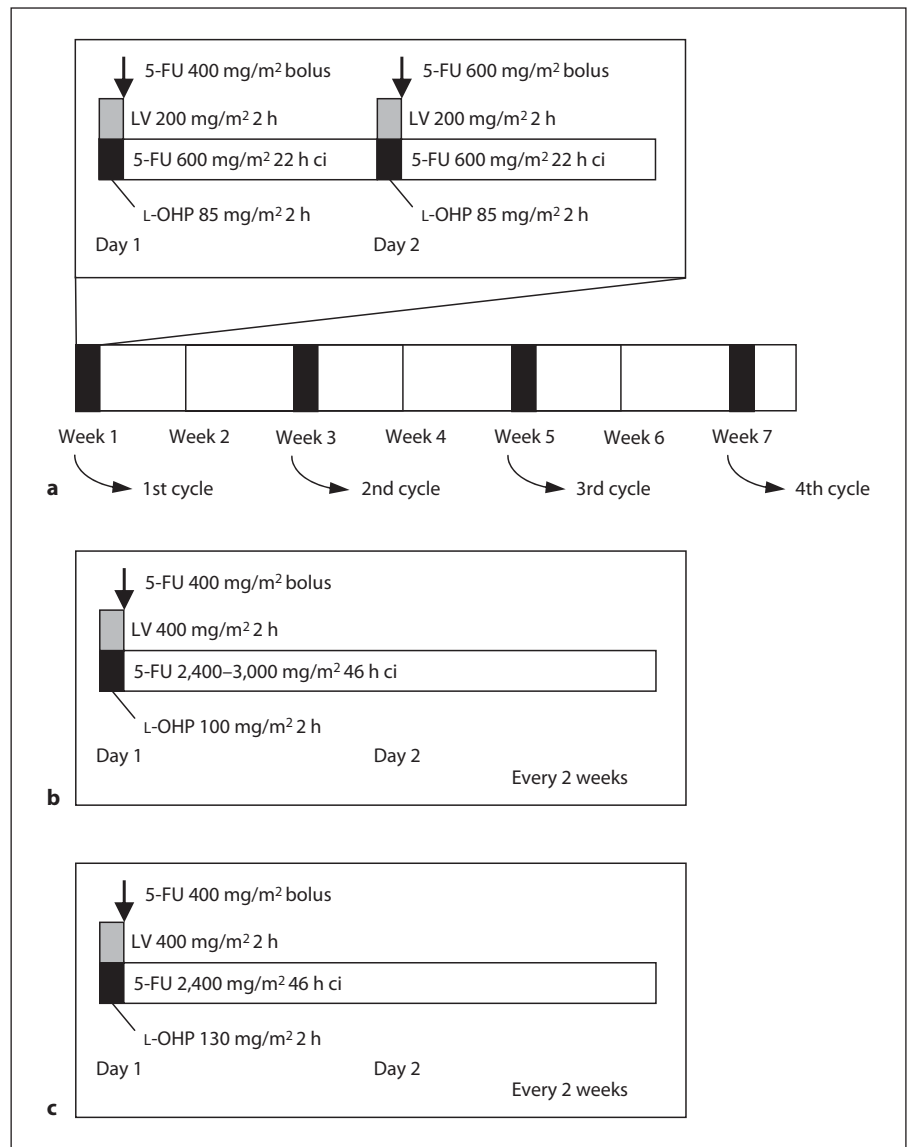


Fig. 2. Drug administration schemata. **a** FOLFOX4. **b** FOLFOX6 (the dose of L-OHP is 85 mg/m² in modified FOLFOX6). **c** FOLFOX7.

mens were developed (fig. 2). FOLFOX4, FOLFOX6, mFOLFOX6 and FOLFOX7 are now used for the treatment of recurrent or metastatic colorectal cancer. mFOLFOX6 is a regimen in which the dose of L-OHP is 85 mg/m², instead of 130 mg/m² in FOLFOX6.

FOLFOX4 is the most common regimen applied to many RCTs. In the first report, of the 57 patients who received FOLFOX4, there were 51 eligible patients and the RR was 23.5% (12/51) [17]. The major toxicities with FOLFOX4 were peripheral neuropathy and neutropenia. The incidence of grade 3–4 neutropenia was 36.9%. The median PFS was 5.1 months and the median OS was 11.1 months.

De Gramont et al. [18] reported the results of an RCT which compared LV5FU2 and FOLFOX as first-line chemotherapy for advanced colorectal cancer. A total of 420 patients were enrolled in the LV5FU2 group (n = 210) and FOLFOX4 group (n = 210). Patients allocated to FOLFOX4 had a significantly longer PFS (median, 9.0 vs. 6.2 months, p = 0.0003) and a better RR (50.7 vs. 22.3%, p = 0.0001) when compared with the control LV5FU2. However, the improvement in OS was not significant (median, 16.2 vs. 14.7 months, p = 0.12).

The clinical effects of FOLFOX regimens have been compared with other regimens, and they are now recognized as one of the first-line chemotherapy regimens for

recurrent or metastatic colorectal cancer. However, it has been pointed out that patients who cannot be reintroduced to the second cycle due to the adverse effect of L-OHP had a bad prognosis. The occurrence of sensory neuropathy is significant because it may cause patients who are continuing to respond to treatment to discontinue treatment. Thus, new regimens, OPTIMOX1 [19] and OPTIMOX2 [19], have been developed to increase the rate of reintroduction without decreasing the clinical effect.

OPTIMOX1 was developed to avoid the problem of neurotoxicity induced by L-OHP so as to eliminate the main factor which disturbs the reintroduction of a regimen containing L-OHP. OPTIMOX1 (arm B) consisted of 6 cycles of dose-intense FOLFOX7 (1 cycle = 2 weeks) followed by 12 cycles of maintenance (LV/5-FU2; 1 cycle = 2 weeks) and subsequent reintroduction of FOLFOX7 for another 6 cycles. OPTIMOX1 was compared with FOLFOX4 (arm A) in previously untreated metastatic colorectal cancer administered until progression or occurrence of unacceptable toxicity [19]. A total of 620 patients were enrolled in this study and randomized to receive arm A (n = 311) and arm B (n = 309). The median PFS were 9.0 and 8.7 months, and the MST were 19.3 and 21.2 months in arm A and arm B, respectively (no significance). The RR were 58.5% in arm A and 59.2% in arm B (no significance). NCI-CTC grade 3 sensory neuropathy was observed in 17.9% of the patients in arm B and in 13.3% of those in arm A (p = 0.12). For the patients who received arm B, oxaliplatin was reintroduced in only 40.1% of the patients but achieved partial response or stable disease in 69.4% of them. According to these results, they concluded that L-OHP could be safely stopped after 6 cycles in a FOLFOX regimen.

In 2007, at the American Society of Clinical Oncology (ASCO) annual meeting, results comparing OPTIMOX1 and OPTIMOX2 in the chemotherapy against metastatic colorectal cancer were reported [20]. OPTIMOX2 was designed to introduce a complete cessation of chemotherapy after FOLFOX. OPTIMOX2 consisted of 6 cycles of FOLFOX7 (total 12 weeks) followed by complete cessation of chemotherapy (chemotherapy-free interval) and reintroduction of FOLFOX7 before the tumor progression reached the baseline. A total of 202 patients were enrolled in this study and randomized to the OPTIMOX1 group (n = 99) and OPTIMOX2 group (n = 103). The median duration of the chemotherapy-free interval in the OPTIMOX2 group was 4.6 months. The RR of OPTIMOX1 and OPTIMOX2 were 63 and 61%, respectively. However, both median PFS and MST of the patients who

received OPTIMOX1 were significantly longer than in those who received OPTIMOX2. The chemotherapy-free interval was not recommended from these results. Further study is needed to fully evaluate stop and go administration of L-OHP.

LV/5-FU/CPT-11 versus LV/5-FU/L-OHP

Goldberg et al. [9] reported the results of an RCT comparing the effects of LV/5-FU/CPT-11, LV/5-FU/L-OHP and CPT-11/L-OHP against metastatic colorectal cancer (N9741). A total of 795 patients were enrolled in this study. IFL was employed as LV/5-FU/CPT-11 (n = 264), FOLFOX4 as LV/5-FU/L-OHP (n = 267), and irinotecan 200 mg/m² and oxaliplatin 85 mg/m² every 3 weeks (IROX) as CPT-11/L-OHP (n = 264). The RR of the patients receiving FOLFOX4 (45%) was significantly higher than for those receiving IFL (31%, p = 0.002) or IROX (35%, p = 0.03). The RR of patients receiving IFL and IROX did not differ (p = 0.34). The time to progression (TTP) was significantly longer for the patients receiving FOLFOX4 (median, 8.7 months) than for those receiving IFL (median, 6.7 months; p = 0.0014). The median TTP for the patients receiving IROX was almost the same as for those receiving IFL (median, 6.5 months, p > 0.50), and the TTP for the patients receiving FOLFOX4 was significantly longer than for those receiving IROX (p = 0.001). The MST for the patients receiving IFL (15.0 months) was significantly shorter than for those receiving FOLFOX4 (19.5 months, p = 0.0001) and those receiving IROX (17.4, p = 0.04 for comparison with IFL). On the other hand, the MST for the patients receiving FOLFOX4 did not differ from the MST of those receiving IROX (p = 0.09). The patients who received IFL had significantly higher rates of diarrhea, vomiting, nausea and febrile neutropenia and significantly lower rates of paresthesias and neutropenia compared with the patients treated with FOLFOX4. The rates of grade 3 or higher toxicity for the patients receiving IROX were similar to those for the patients receiving IFL. The second-line treatments were not specified by the protocol in this study. A high proportion (60%) of the patients treated with FOLFOX4 received CPT-11 as the second-line therapy, and fewer patients (24%) receiving IFL were treated with L-OHP regimens as the second-line therapy. Regardless, the results of N9741 showed the superiority of FOLFOX4 compared with IFL and IROX in the treatment of metastatic colorectal cancer.

Tournigand et al. [21] reported the results of an RCT comparing FOLFIRI followed by FOLFOX6 (arm A) and the reverse sequence, FOLFOX6 followed by FOLFIRI (arm B) in the treatment of advanced colorectal cancer. A total of 226 patients were randomly assigned with 113 in each arm. In the first-line therapy, 3 complete responses were observed with FOLFIRI (2.8%) and 5 with FOLFOX6 (4.5%). The RRs were 56% with FOLFIRI and 54% with FOLFOX6 (not significant). The median response time was 11 months for arm A and 10.6 months for arm B. In the second-line therapy, the RRs were 15% with FOLFOX6 (arm A) and 4% with FOLFIRI (arm B). The arm A patients received a median of 8 cycles (2–23 months) of FOLFOX6, and those in arm B received a median of 6 cycles (1–33 months) of FOLFIRI as the second-line therapy. There were no chemotherapy-related deaths. The median OS was 21.5 months for arm A and 20.6 months for arm B ($p = 0.99$). From these results, FOLFIRI and FOLFOX are now considered to have almost the same efficacy in the treatment of advanced or metastatic colorectal cancer when another regimen is used as the second-line therapy. It is important to use all of LV/5-FU, CPT-11 and L-OHP in the treatment of advanced or metastatic colorectal cancer to achieve adequate clinical results. FOLFIRI followed by FOLFOX or FOLFOX followed by FOLFIRI provide about 21 months of MST in advanced or metastatic colorectal cancer.

Molecular Targeting in Chemotherapy against Advanced, Recurrent or Metastatic Colorectal Cancer

VEGF is a proangiogenic growth factor, and has a crucial role in physiological and pathological angiogenesis. VEGF regulates both vascular proliferation and permeability and functions as an antiapoptotic factor for newly formed blood vessels. Angiogenesis is required for tumor growth and metastasis. Abnormal angiogenesis in cancer is characterized by excessive neovascularization. Consequently, VEGF represents an exciting target for cancer treatment [22].

Bevacizumab (Avastin®) is an anti-VEGF monoclonal antibody [23]. Bevacizumab decreases tumor perfusion, vascular volume, microvascular density, interstitial fluid pressure and the number of viable, circulating endothelial cells [24].

Bevacizumab plus 5-FU/LV has resulted in a higher response and longer survival than 5-FU/LV alone in first-line metastatic colorectal cancer [25]. Hurwitz et al. [26]

reported the results of an RCT to investigate the additional effects of bevacizumab on IFL in the treatment of metastatic colorectal cancer. A total of 813 patients with previously untreated metastatic colorectal cancer were randomly assigned to receive IFL plus bevacizumab 5 mg/kg every 2 weeks ($n = 402$) and to receive IFL plus placebo ($n = 411$). The MST was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 ($p < 0.001$). The median duration of PFS was also significantly prolonged in the IFL plus bevacizumab group as compared with the IFL plus placebo group ($p < 0.001$), and the RR in the IFL plus bevacizumab group (44.8%) was significantly higher compared with that in the IFL plus placebo group (34.8%, $p = 0.004$). Bevacizumab with FOLFOX4 or capecitabine/L-OHP (XELOX) has also been reported to prolong PFS significantly compared with a placebo and chemotherapy (10.4 vs. 7.9, $p = 0.0023$) [27]. In subgroup analysis, a significant additional effect of bevacizumab has been observed with XELOX but not with FOLFOX4. However, another study showed that bevacizumab had a synergistic effect with FOLFOX [28].

Bevacizumab is now approved in the first- or second-line chemotherapy against advanced or metastatic colorectal cancer with LV/5-FU, IFL, FOLFOX4 or XELOX [25–28]. However, the adverse effects of bevacizumab, including deep vein thrombosis and perforation of gastrointestinal tract, cannot be disregarded [29]. As the clinical effects provided by bevacizumab are not so large, further examination is needed regarding the merits and demerits of this expensive drug.

VEGF is a protein tyrosine kinase expressed on many types of tumor cell, including colorectal, breast and ovarian cancer cells [30]. There seems to be an association between upregulation of EGFR and poor clinical outcome and prognosis for human cancers. Cetuximab (Erbix®) is a chimeric antibody consisting of a highly specific murine monoclonal antibody component that binds specifically to human EGFR with an affinity equal to its ligand and human IgG1 [30]. Cetuximab competes with the ligand for binding and blocks the activation of the EGFR tyrosine kinase.

Cetuximab showed disease control effects in tumors that had been refractory to CPT-11, L-OHP and 5-FU when used with CPT-11 [31]. In most of the clinical trials with cetuximab, a correlation between response and its main toxicity, an acne-like skin reaction, has been observed.

Table 1. Summarized advances in the first-line chemotherapy against advanced or metastatic colorectal cancer

Authors	Regimens	Patients	RR, %	OS, months
Scheithauer et al. [1], 1993	BSC	12	–	5
	LV/5-FU/cisplatin	24	–	11
Thirion et al. [4], 2004	5-FU	meta-analysis	11	10.5
	LV/5-FU	21 RCTs	21	11.7
Saltz et al. [12], 2000	LV/5-FU	226	21	12.6
	LV/5-FU/CPT-11 (IFL)	231	39	14.8
	CPT-11	226	18	12.0
De Gramont et al. [18], 2000	LV5FU2	210	22.3	14.7
	FOLFOX4	210	50.7	16.2
Goldberg et al. [9], 2004	IROX	264	35	17.4
	IFL	264	31	15.0
	FOLFOX4	267	45	19.5
Tournigand et al. [21], 2004	FOLFIRI → FOLFOX6	113	56	21.5
	FOLFOX6 → FOLFIRI	113	54	20.6
Hurwitz et al. [26], 2004	IFL + Ava	402	44.8	20.3
	IFL + Plac	411	34.8	15.6
Saltz et al. [27], 2007	FOLFOX4 or Cape + Ava	699	38	10.4 (PFS)
	FOLFOX4 or Cape + Plac	701	38	7.9 (PFS)
Van Cutsem et al. [32], 2007	FOLFIRI + Cet	608	46.9	8.9 (PFS)
	FOLFIRI + Plac	609	38.7	8.0 (PFS)
Bokemeyer et al. [33], 2007	FOLFOX + Cet	169	45.6	NR
	FOLFOX + Plac	168	35.7	NR

Ava = Bevacizumab; Cet = cetuximab; Cape = capecitabine; Plac = placebo; NR = not reported. Thirion et al.: analyzed RCTs were reported between 1987 and 2003.

Recently, the combination effect of cetuximab as the first-line therapy against metastatic colorectal cancer with FOLFIRI or FOLFOX has been proven. Van Cutsem et al. [32] reported the results of the CRYSTAL trial in ASCO 2007. In the CRYSTAL trial, 1,217 EGFR-expressing metastatic colorectal patients were randomized to receive either cetuximab (400 mg/m² initial dose, then 250 mg/m²/week) plus FOLFIRI (group A, n = 608) or FOLFIRI alone (group B, n = 609). The median PFS was significantly longer for group A compared to group B (8.9 vs. 8.0 months, *p* = 0.036). The RR was also significantly increased by cetuximab (46.9 vs. 38.7%, *p* = 0.005). Cetuximab in combination with FOLFIRI significantly increases the RR and significantly prolongs PFS in the first-line treatment of metastatic colorectal cancer.

Bokemeyer et al. [33] reported the results of the OPUS study. In the OPUS study, 337 patients with previously untreated EGFR-expressing metastatic colorectal cancer were enrolled. They were randomized to receive FOLFOX4 plus cetuximab (400 mg/m² dose, then 250 mg/m² every 2 weeks, group A, n = 169) or FOLFOX4 alone

(group B, n = 168). The overall RR was 45.6% in group A and 35.7% in group B. The disease control rate was 85.2% in group A and 81.0% in group B. The RR for the patients with grade 3 skin rash (n = 24) was 66.7%. On the other hand, the RR for the patients with grade 0 skin rash (n = 23) was 13%. The addition of cetuximab increased the RR of FOLFOX4 in the first-line treatment of metastatic colorectal cancer. The severity of the skin rash also correlated to the clinical effects in this combination. Cetuximab is likely to be effective in the first-line chemotherapy against metastatic colorectal cancer with FOLFIRI or FOLFOX (table 1).

Saltz et al. [34] reported the effect of cetuximab (with or without CPT-11) as second-line therapy in patients who failed CPT-11 in combination with bevacizumab (BOND-2 study). The BOND-2 study was a randomized phase II trial in patients with CPT-11-refractory colorectal cancer. All patients were naïve to both bevacizumab and cetuximab. The patients in arm A received CPT-11 at the same dose and schedule as last received before study entry, plus cetuximab at a 400 mg/m² loading dose, then

weekly cetuximab 250 mg/m², plus bevacizumab 5 mg/kg administered every other week (CBI). The patients in arm B received the same cetuximab and bevacizumab as those in arm A but without CPT-11 (CB). Forty-three patients received CBI, and 40 patients received CB. For the CBI arm, the TTP was 7.3 months and the RR 37%; for the CB arm, the TTP was 4.9 months and the RR was 20%. The OS for the CBI arm was 14.5 months and the OS for the CB-alone arm 11.4 months. The CBI showed this feasible for second-line therapy against colorectal cancer, and its activity appeared favorable.

Medical Economics in the Chemotherapy against Colorectal Cancer

Monoclonal antibody agents, including bevacizumab and cetuximab, are very expensive. Consequently, even if they demonstrate significant activity in advanced or metastatic colorectal cancer, it is necessary to estimate the cost-effectiveness of adding these agents to chemotherapy for colorectal cancer.

Tappenden et al. [35] estimated the cost-effectiveness of additive bevacizumab and/or cetuximab in the chemotherapy for untreated metastatic colorectal cancer with a systematic review. This independent health economic assessment suggests that the cost-effectiveness of bevacizumab plus IFL is unlikely to be better than GBP 46,853 per life-year gained and the cost-utility of bevacizumab plus IFL is unlikely to be better than GBP 62,857 per quality-adjusted life-year (QALY) gained. The cost-utility of bevacizumab plus LV/5-FU versus LV/5-FU is also unlikely to be better than GBP 88,658 per QALY gained.

There is no direct evidence to demonstrate whether cetuximab in combination with CPT-11 improves health-related quality of life in comparison to BSC or FOLFOX. Consequently, it is difficult to confirm whether cetuximab represents value for money. However, indirect comparisons suggest that the incremental cost-utility of cetuximab plus CPT-11 is unlikely to be better than GBP 30,000 per QALY gained. For the very high acquisition costs in relation to clinical benefits, the antibody agents bevacizumab and cetuximab are unlikely to represent cost-effectiveness or cost-utility.

Future Perspectives in the Chemotherapy against Colorectal Cancer

Combination chemotherapy regimens, including FOLFIRI and FOLFOX, have prolonged the survival of advanced or metastatic colorectal cancer patients 3- to 4-fold compared with BSC alone. Additional monoclonal antibody agents provide little additive utility at high cost. New agents, including new macromolecule agents, small-molecule agents and vaccines, will be introduced in the chemotherapy against colorectal cancer. Subsequently, clinical researchers will have to consider the cost-utility of these agents using QALY.

Disclosure Statement

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