Original Article

Comparison of Efficacy of Panitumumab in Combination with Oxaliplatin-based versus Irinotecan-based Chemotherapy

Chia-Hung Chen[1]
Ling-Chiao Song[1]
Chih-I Chen[1,2,3,4,5]
Hsin-Pao Chen[1,3]
Kuang-Wen Liu[1,3]
[1]*Division of Colon and Rectal Surgery,*
[2]*Divsiion of General Medicine Surgery, Department of Surgery, E-DA Hospital,*
[3]*School of Medicine, College of Medicine,*
[4]*Department of Information Engineering,*
[5]*The School of Chinese Medicine for Post Baccalaureate, I-Shou University, Kaohsiung, Taiwan*

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Purpose. Patients with metastatic colorectal cancer (mCRC) are faced with poor prognosis. It is well-established that the addition of panitumumab (Pmab) to conventional chemotherapy is able to achieve survival benefit in such patients. However, the comparison of efficacy of Pmab with oxaliplatin-based chemotherapy agent (Pmab-OX) and Pmab with irinotecan-based chemotherapy agent (Pmab-IRI), in a real-world situation required further investigations.

Methods. The study collected cases of Rat sarcoma viral oncogene homologue (RAS) wild-type (WT) mCRC receiving first-line treatment with either Pmab-OX or Pmab-IRI in E-Da Hospital and E-DA Cancer Hospital between 2017 and 2021. The primary end-point measured was the objective response rate (ORR). Secondary end points included progression-free survival (PFS), overall survival (OS), and colorectal liver metastasis (CRLM) resection rate.

Results. 21 patients with wild-type RAS (WT-RAS) mCRC receiving first-line Pmab with conventional chemotherapy were recruited. The ORR was 33% in both Pmab-OX and Pmab-IRI groups. Mean PFS of Pmab-OX and Pmab-IRI were 29 months and 30 months, respectively. Mean OS of Pmab-OX and Pmab-IRI were 34 months and 30 months, respectively. The liver resection rate in the CRLM-only patients after panitumumab treatment was 43%.

Conclusions. In the WT-RAS mCRC patients, first-line Pmab-OX and Pmab-IRI showed similar efficacy, where no statistically differences in ORR, PFS, and OS were observed. However, due to the small sample size and the follow-up time being less than 5 years in all the cases, further studies will be needed to determine the efficacy of Pmab-OX and Pmab-IRI.

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In 2020, colorectal cancer is ranked as the third most common cancer and second in terms of mortality, with more than 1.9 million newly diagnosed cases per year and 935,000 related deaths.[1] Approximately 25% of colorectal cancers are metastatic at initial diagnosis.[2] Patients with metastatic colorectal cancer (mCRC) have a poor prognosis, with a five-year survival rate of 15%, compared to 72% in regional and 91% in localized CRC in the United States.[3]

Systemic therapy, by the use of cytotoxic and molecular targeting agents combination, is currently the most suitable treatment for patients with mCRC. Such

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Correspondence to: Dr. Ling-Chiao Song, Division of Colon and Rectal Surgery, Department of Surgery, E-DA Hospital, No. 1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung 82445, Taiwan. Tel: 886-7-615-0011; Fax: 886-7-615-5352; E-mail: kulairumi@gmail.com

therapy has demonstrated survival benefits and improvement in the quality of life of patients.[4] Conventional chemotherapy by combining 5-fluorouracil with either oxaliplatin (OX) or irinotecan (IRI) has become the backbone for mCRC treatment.[5] A meta-analysis conducted by Grothey et al. suggested all three drugs are correlated with increase in overall survival.[6]

Currently approved targeted therapies include epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, and VEGF receptor inhibitors, have also become available for the treatment of mCRC.[7] Anti-EGFR monoclonal antibodies, such as panitumumab and cetuximab, have been commonly used in combination with chemotherapy for patients with wild-type RAS (WT-RAS) mCRC.[8-10] In the Central European Co-operative Oncology Group (CECOG) trial, first-line treatment with either cetuximab-FOLFOX6 or cetuximab-FOLFIRI on unresectable CRLM patients demonstrated better survival outcomes in tumors without KRAS mutations than tumors with KRAS mutation.[8] The efficacy of panitumumab in first-line and second-line treatment has been well-established.[11] When combined with Ox-based chemotherapy agent or irinotecan-based chemotherapy, panitumumab displayed improved outcome in a real-world situation still need to be further examined.

This study aimed to investigate the efficacy of panitumumab when combined with Ox-based chemotherapy agent or irinotecan-based chemotherapy in WT-RAS patients. The objective response rate (ORR), which include complete response and partial response, was selected as the primary endpoint in this study. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and CRLM-only resection rate after the initiation of panitumumab treatment.

Materials and Methods

Patient selection

This retrospective cohort study included patients with WT-RAS mCRC who had undergone first-line treatment with Pmab plus conventional chemotherapy in E-DA Hospital and E-DA Cancer Hospital between January 2017 and December 2021.

Patients with histologically confirmed WT-RAS mCRC were eligible for inclusion. There was no restrictions on the site of metastasis. However, only the individuals who received first-line regime with conventional chemotherapy and at least six cycles of Pmab were included. Patients who received regime other than Pmab-OX and Pmab-IRI or less than six cycles of Pmab were excluded from the study.

All study procedures were performed in accordance to the accepted ethical standards.

Study treatment

The patients were administered Pmab (6 mg/kg) every 2 weeks with FOLFOX7, FOLFIRI, or XELOX (Oxaliplatin 130 mg/m^2 every 2 weeks + oral Capecitabine 850-1000 mg/m^2 twice a day for 14 consecutive days). After completion of 6 cycles from the initiation of the first cycle, computed tomography was done to assess the response of the treatment. If there was no disease progression or death from any cause, informed consent will be obtained from the patient to receive additional cycles.

In initially unresectable CRLM-only patients, if tumor shrinkage and resectability was achieved after at least 6 cycles of treatment, a combined meeting with general surgeon will be held to discuss the feasibility of hepatectomy. If curative resection of liver metastases was deemed possible, hepatectomy will be performed after the patient's informed consent. If, however, the patient refused surgical approach, radiofrequency ablation (RFA) may be done as an alternative at the patient's choosing.

Patient grouping and end points

The patients receiving Pmab with chemotherapy were divided into two groups. The first group include patients using an OX-based agent and the second group include those using an IRI-based agent. After completion of at least 6 cycles of combination regime, tumour response was assessed in accordance to the hospital guideline set by a multidisciplinary team. Objec-

tive tumour response to treatment, measured based on the New response evaluation criteria in solid tumours (RECIST version 1.1) guidelines, were divided into complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD).[12] ORR included tumors with CR and PR.

Statistical analysis

The primary endpoint of this study was the ORR (complete response + partial response). The objective response was assessed after at least 6 Pmab cycles. Secondary endpoints included OS and PFS. OS and PFS were defined as the time from the first Pmab administration to death from any cause and disease progression, respectively. Another endpoint was the rate of liver metastases treatment in CRLM-only patients after 6 cycles of Pmab, which included those underwent either hepatectomy or RFA therapy.

The patients were followed up until 31st March 2022. Data analysis was done using SPSS statistics 26 package. The end points were expressed using descriptive statistics, 95% confidence intervals (CI), and Kaplan-Meier plots. The median survival was the smallest time at which the survival probability drops to 0.5 (50%) or below. If survival probability curve did not drop to 0.5 or less, median cannot be computed. Thus, mean OS and PFS were calculated instead.

Results

Patient- and cancer-related characteristics

21 patients (16 men and 5 women) with WT-RAS mCRC were enrolled in this study between January 2017 and November 2021. The median age of the patients at diagnosis in both arms were 69 years old, ranging from 33 to 86 years old in the Pmab-OX arm and 48 to 86 years old in the Pmab-IRI arm. The Pmab-OX group included 15 patients (14 patients using FOLFOX and 1 patient using XELOX) and Pmab-IRI group included 6 patients using FOLFIRI. The Pmab-IRI group had a proportion of colon cancer than rectal compared to the Pmab-OX group (83% vs. 60%). The remaining baseline patient characteristics were similar between the 2 arms (Table 1). Only 2 patients had primary tumour over right side.

The median follow-up time was 18.5 months (range, 6-45 months). The treatment responses, which were assessed after 6 cycles of treatment initiation, were assigned to the following categories: complete response (0/21, 0%), partial response (7/21, 33.3%), stable disease (9/21, 42.8%), progressive diseases (2/21, 9.5%).

Efficacy study

In evaluating the 21 WT-RAS mCRC patients, the ORR of the Pmab-OX and Pmab-IRI were the same

Table 1. Baseline characteristics of the WT-RAS mCRC population

Characteristic	Pmab-OX (n = 15)	Pmab-IRI (n = 6)
Sex, no. (%)		
Male	12 (80)	4 (67)
Female	3 (20)	2 (33)
Median age, years (min,max)	67 (33,81)	67(48,86)
Primary tumour location, no. (%)		
Colon	9 (60)	5 (83)
Rectum	6 (40)	1 (17)
TMN stage at diagnosis, no. (%)		
II	3 (20)	1 (17)
III	3 (20)	2 (33)
IV	9 (60)	3 (50)
Prior surgery for primary tumour, no. (%)	11 (73)	4 (67)
Site of metastases, no. (%)		
Liver only	7 (47)	4 (67)
Liver + other organs	6 (40)	1 (17)
Other organs without liver	2 (13)	1 (17)
Baseline CEA level, no. (%)		
< 5 mg/dL	4 (27)	1 (17)
≥ 5 mg/dL	11 (73)	5 (83)
Tumour response, no. (%)		
CR	0 (0)	0 (0)
PR	5 (33)	2 (33)
SD	9 (60)	3 (50)
PD	1 (7)	1 (17)

Pmab-OX = panitumumab with oxaliplatin-based agent; Pmab-IRI = panitumumab with irinotecan-based agent; CEA = carcinoembryonic antigen; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

(33% vs. 33%; $p = 1$) (Table 2); no complete response was observed. 5 patients with PR (5/15) were noted in the Pmab-OX group, while 2 patients with PR (2/6) were noted in Pmab-IRI group.

Mean PFS between the 2 arms were comparable, 29 months (95% CI: 19-38) in Pmab-OX and 30 months (95% CI: 22-38) in Pmab-IRI (Fig. 1). Mean OS was 34 months (95% CI: 25-43) in Pmab-OX and 30 months (95% CI: 22-38) in Pmab-IRI, without significant differences between the 2 arms (Fig. 2).

Table 2. Efficacy of Pmab-OX versus Pmab-IRI in WT-RAS mCRC patients

	Pmab-OX (n = 15)	Pmab-IRI (n = 6)	p value
ORR	33 (11-61)	33 (4-77)	1
PFS	29 (19-38)	30 (22-38)	0.429
OS	34 (25-43)	30 (22-38)	0.705

ORR = objective response rate (complete response + partial response); PFS = progression-free survival; OS = overall survival.

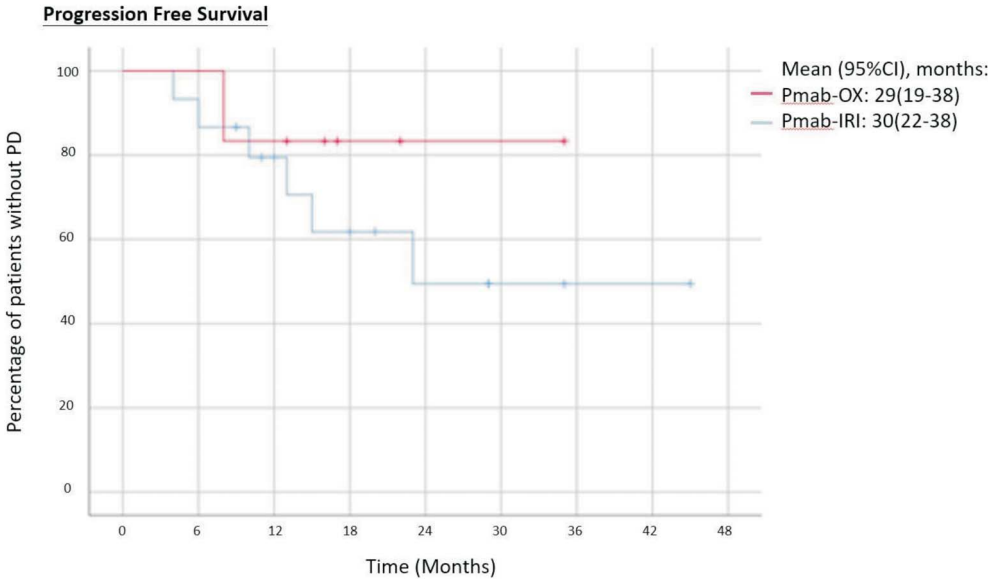

Fig. 1. Progression-free survival in the WT-RAS population.

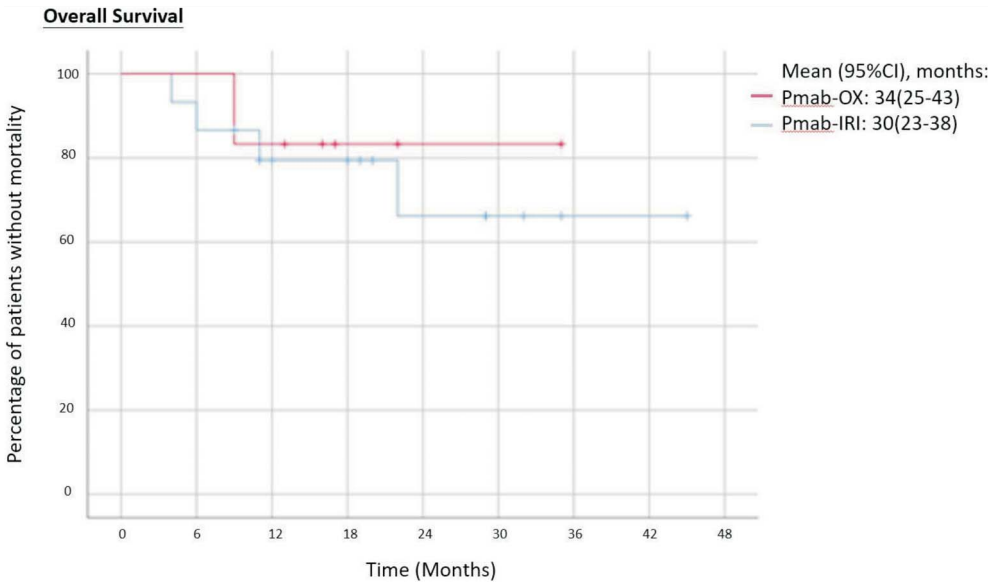

Fig. 2. Overall survival in the WT-RAS population.

CRLM treatment

Out of the 11 CRLM-only patients, 2 patients underwent RFA and 2 patients had hepatectomy prior to chemotherapy. In the remaining 7 patients who exhibited initial unresectable liver metastases, 3 underwent hepatectomy after completion of at least 6 Pmab cycles, with an overall resection rate of 43% (Table 3). In the Pmab-OX arm, there were 5 initially-unresectable CRLM-only patients, of which 3 achieved resectability and underwent hepatectomy, with a subgroup resection rate of 60%. Whereas in the Pmab-IRI arm, there were 2 initially-unresectable CRLM-only patients, both remained unresectable up until the followed-up time. In the CRLM-only subgroup, the PFS was 21 months in Pmab-OX and 28 months in Pmab-IRI, while OS was 26 months in Pmab-OX and 28 months in Pmab-IRI (Fig. 3 and Fig. 4).

Discussion

Cytotoxic agents with IRI and OX have become the backbone in treatment of the patients with mCRC. Comparison of the two agents have been extensively studies. Phase III studies conducted by Tournigand et al.[13] and Colucci et al.[14] comparing FOLFOX and FOLFIRI regimens concluded that both treatments are able to achieve survival benefits and with similar efficacy. A meta-analysis, by Kawai et al., comparing first-line therapies with IRI- and OX-based regimens in mCRC demonstrated similar OS, PFS, and ORR between the two arms.[15]

Pmab, when added to either FOLFOX[10] or FOLFIRI,[16] has proven to have survival benefits. In PRIME (Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy), a randomized, multicenter, phase III trial, which compared the first-line treatment of mCRC using Pmab-FOLFOX4 and FOLFOX4 alone, a 60% ORR (% difference: 13.7%, 95% CI: 5.0-22.4) in the Pmab-FOLFOX4 arm and 47% ORR (% difference: 15.0%, 95% CI: -3.40-33.4) in FOLFOX4 arm was observed.[10] A phase III trial conducted by Peeters et al. showed significantly improved ORR in the Pmab-FOLFIRI group compared to FOLFIRI alone group in patients with WT-KRAS tumors.[16] However, which chemotherapy backbone would provide the better efficacy in mCRC patients required further evaluations. A randomized phase II trial (PLANET-TTD), compared the efficacy of first-line Pmab in combination with either FOLFOX4 or FOLFIRI in patients with WT-RAS mCRC, demonstrated an ORR of 74% (95% CI: 60-88) with Pmab-FOLFOX4 and 67% (95% CI: 52-82) with Pmab-FOLFIRI.[17] In our study, Pmab-OX demonstrated an ORR of 33% and Pmab-IRI also had an ORR of 33% (95% CI: 11-61). The PLANET-TTD trial collected patients with liver-limited disease (LLD),[17] whereas our study included patients with metastasis to various distant organs. It is well recognized that metastatic spread to more than one distant organ results in worse survival outcomes compared to LLD in CRC patients, [18] which could account for the lower ORR observed in our study.

In the PLANET-TTD trial, the median PFS of Pmab-FOLFOX4 and Pmab-FOLFIRI were 13 months (95% CI: 6-19) and 15 months (95% CI: 7-19), respectively; while the median OS were 39 (95% CI: 27-51) and 49 months (95% CI: 31-56), respectively.[17] The PRIME trial showed a median PFS of 11.1 months (95% CI: 7-19) and OS of 26.0 months in patients with LLD receiving Pmab + FOLFOX4.[10] In our study, the mean PFS were in Pmab-OX and Pmab-IRI were 29 months (95% CI: 19-38) and 30 months (95% CI: 22-38), respectively; while the mean OS were 34 months (95% CI: 25-43) and 30 months (95% CI: 32-38). When only considering the LLD subgroup, the PFS in Pmab-OX and Pmab-IRI were 21 months (95% CI: 14-28) and 28 months (95% CI: 17-39), respectively; while OS were 26 months (95% CI: 19-33) and 28 months (95% CI: 17-39). Despite having multiple metastasis patients in our study, the data from PFS or

Table 3. Efficacy of Pmab-OX versus Pmab-IRI in CRLM-only patients

	Pmab-OX (n = 5)	Pmab-IRI (n = 2)	p value
ORR	14 (3-57)	25 (6-80)	1
Hepatectomy	60 (9-81)	0	0.236
PFS	21 (14-28)	28 (17-39)	0.729
OS	26 (19-33)	28 (17-39)	0.919

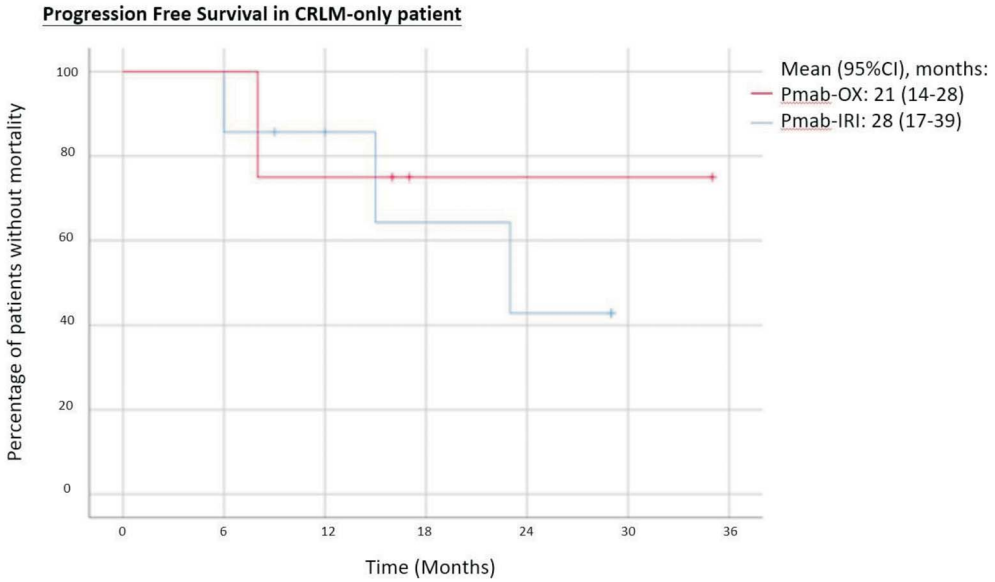

Fig. 3. Progression-free survival in the CRLM-only WT-RAS population.

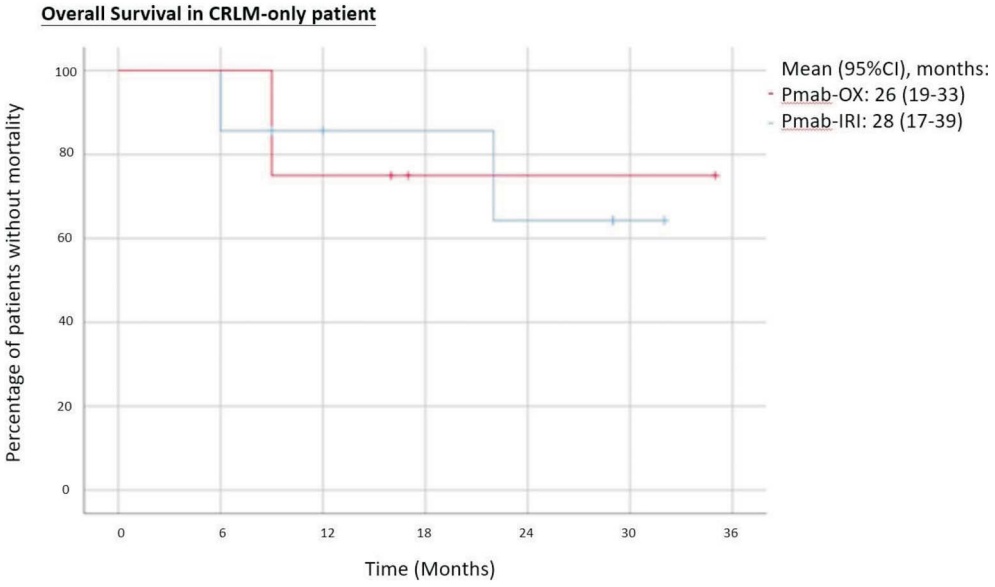

Fig. 4. Overall survival in the CRLM-only WT-RAS population.

LLD-specific PFS, both were considerably longer than previous studies. However, our OS result was shorter when compared to reported studies. The PFS and OS number in our study were quite close, which is due to the short follow-up time where a majority of the patients have not yet reached mortality.

Studies that explore the efficacy of first-line cetuximab with chemotherapy combination also presented with similar efficacy. In FIRE-3 trial, comparing the efficacy of first-line cetuximab-FOLFIRI versus bevacizumab-FOLFIRI in WT-RAS mCRC patients, cetuximab had an ORR of 77%.[19] TAILOR, an open-label, randomized phase III trial comparing FOLFOX-4 with or without cetuximab in WT-RAS mCRC, demonstrated an ORR of 61% with cetuximab-FOLFOX4.[20] These results are comparable to studies with Pmab as the target agent.

The main objective of therapy in CRLM-only mCRC is to achieve complete resection of the liver metastases, which was proven to have good long-term

cancer-specific survival benefit.[21] In a study conducted by Folprecht et al., a strong correlation was found between response rates and the resectability of liver metastases in patient with LLD.[22] Thus, in order to increase survival in LLD patients, cancer shrinkage to achieve resectable CRLM becomes vital. The subgroup with initially unresectable metastases in PLANET-TTD trial demonstrated a resection rate of 26% in Pmab-FOLFOX4 (95% CI: 9-42) and 54% in Pmab-FOLFIRI (95% CI: 35-73).[16] The PRIME trial demonstrated a 31% resection rate (% difference: 14.2, 95% CI: -3.3-31.6) in LLD patients who received Pmab-FOLFOX4.[10] In CELIM, a multi-centred, randomized phase II trial, patients with initially unresectable CRLM received either cetuximab-FOLFOX or cetuximab-FOLFIRI, an overall 34% R0 resection rate (36/106) was achieved after treatment.[23] In comparison, our study showed a overall resection rate of 43% (3/7) and resection rate in Pmab-OX of 60% (3/5), which were non-inferior. However, the limited patient number in the Pmab-IRI LDD subgroup resulted in a 0% resection rate (0/2).

The main limitation of this study is the small sample size and lack of follow-up time. Pmab was introduced into our hospital in January 2017. Since then, 21 patients fit our inclusion criteria and were recruited into the study. Only 5 of these patients had followed up for more than 3 years.

Although certain trends can be perceived, the small patient size prevented us from drawing definite conclusions, especially in the subgroups. These limitations could account for the relatively low OS that was observed compared to those in previously reported studies. The absence of statistical differences may be attributed to the lack of power in this trial.

Conclusion

The addition of Pmab to first-line chemotherapy agent offered improvement in ORR, OS, PFS, and secondary resection rate in WT-RAS mCRC patients. No statistical differences in efficacy between the Pmab-OX and the Pmab-IRI regimens were observed. In the CRLM-only patients, treatment with Pmab was able to achieve a higher liver resection rate, hence improving the survival outcome of the patient. The limitations attributed to the sample size and follow-up time may be corrected by continuous future investigations.

Disclosure

The authors reported no conflicts of interest in this work.

Sources of Financial Support

None.

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原　著

Panitumumab 合併 Oxaliplatin 類及 Irinotecan 類化療藥物之療效比較

陳嘉宏[1]　陳致一[1,2,3,4,5]　陳興保[1,3]　劉廣文[1,3]　宋翎巧[1]

[1]義大醫院　外科部　大腸直腸外科

[2]義大醫院　外科部　一般醫學外科

[3]義守大學　醫學系

[4]義守大學　資訊工程系

[5]義守大學　學士後中醫學系

目的　大腸癌診斷時已經轉移之案例其預後非常差，雖然已證實全身性化療能有效延長存活，但預後還是不好。近年來許多國家開始在治療上搭配標靶藥物使用，同時使用 panitumumab (Pmab) 已被證實可有效增加存活率，本研究在轉移性 wild-type RAS 大腸癌之患者上使用 Pmab，並合併含 oxaliplatin (OX) 或 irinotecan (IRI) 之化療藥物，在兩者的使用經驗上來做比較。

研究方法　研究收集 2017~2021 年間義大醫院及義大癌治療醫院轉移性 WT-RAS 大腸癌之患者，在第一線含 oxaliplatin 或 irinotecan 之化療藥物中加入 Pmab 治療上做比較。主要療效指標為客觀緩解率 (objective responserate, ORR)。次要療效指標包括無惡化存活期 (progression-freesurvival, PFS)、整體存活率 (overall survival, OS)、和肝轉移切除率 (liver metastases resection rate)。

結果　此研究共收集 21 名患者。兩者化療藥物加 Pmab 的 ORR 同樣為 33%，Pmab-OX 及 Pmab-IRI 之疾病無惡化存活期分別為 29 個月及 30 個月；而總生存率為 34 個月及 30 個月。在單獨肝轉移之病人上使用 Pmab 後的肝切除率為 43%。

結論　在 WT-RAS mCRC 患者上，在無論所選為含 oxaliplatin 或 irinotecan 之化療藥物中，加入 Pmab 都顯著的改善 ORR，Pmab-OX 及 Pmab-IRI 的比較下，ORR、PFS 及 OS 都沒有顯著的差異。然而，由於樣本量小和追蹤時間都少於 5 年，尚無法定論長期下來之結果是否會有差異，未來更長期的追蹤研究是必是需要的。

關鍵詞　大腸直腸癌、標靶治療、panitumumab、oxaliplatin、irinotecan。