Original Article

EGFR Target as First Line Treatment for K-RAS Wild Type Patients: The Analysis of OPTIM1SE Study at the National Cheng Kung University Hospital

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Key Words
5-fluorouracil;
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Aim. This study aimed to analyze the participants from the OPTIM1SE study conducted at National Cheng Kung University Hospital (NCKUH) in Tainan, Taiwan, and determine the differences in the treatment effect between NCKUH data and global data.
Methods. This prospective, observational, open-label study was conducted at NCKUH in Tainan, Taiwan. Participants who had untreated histologically proven colon or rectal adenocarcinoma with distal metastasis and had KRAS wild-type status and follow-up at least 3 years between April 2014 and June 2016 were recruited. The primary outcome of the study was the overall response rate (ORR). Secondary outcomes comprised progression-free survival (PFS) and overall survival (OS). The conversion rate of unresectable tumors to resectable ones was measured.
Results. Twenty-eight patients who met the criteria were enrolled in the OPTIM1SE trial at NCKUH. The ORR was 64.3%, with 16 patients (57.1%) showing a partial response and 2 (7.1%) achieving a complete response. The median PFS for these 28 patients was 12 (95% CI 8-26) months, and the median OS was 28 (95% CI 16-45) months. Of the 28 patients, 12 received metastatic tumor resection and 4 were initially unresectable but later became resectable after receiving cetuximab-based 5-FU regimen. Overall, the safety of the cetuximab-based 5-FU regimens was generally manageable, with no fatalities.
Conclusion. The results of the OPTIM1SE study and our analysis at NCKUH contribute to more evidence supporting the use of cetuximab-based 5-FU chemotherapy regimen as a first-line treatment option for patients with RAS wild-type metastatic colorectal cancer.

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Colorectal cancer (CRC) is the most prevalent cancer in Taiwan, which occurs in 16826 per 100,000 people, and ranks as the third leading cause of cancer-related deaths in the country in 2020.[1] Early-stage CRC without evident metastasis is typically treated with curative surgery, whereas metastatic CRC (mCRC) requires systemic chemotherapy combined with targeted therapy over curative surgery.[2] The mutational status of the RAS gene serves as a predictive factor for the response to epidermal growth factor re-

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ceptor (EGFR) inhibitor-based regimens, such as cetuximab or panitumumab, in mCRC.[2]

According to the 2023 NCCN treatment guidelines, the standard treatment regimens for RAS wild-type mCRC consist of combinations of 5-fluorouracil (5-FU), leucovorin, and irinotecan/oxaliplatin (FOLFIRI/FOLFOX) with an EGFR inhibitor or a vascular endothelial growth factor inhibitor (e.g., bevacizumab).[3]

Cetuximab (Erbitux®) is a monoclonal antibody that belongs to the IgG1 class and is a recombinant chimeric human/mouse antibody. It targets and binds to the EGFR, competitively inhibiting the binding of epidermal growth factor (EGF) and other ligands to the receptor. Consequently, the EGFR signaling pathway is inhibited, leading to the suppression of cell cycle progression, cell survival pathways, tumor cell motility, and invasion. In addition, cetuximab can enhance the effects of other treatments such as irinotecan therapy and radiotherapy, making it a valuable component in combination therapy for mCRC.[4]

The OPTIMISE study, conducted in a real-world setting, provided additional evidence supporting the efficacy and safety of cetuximab-based 5-FU regimens as first-line treatment options for mCRC. According to the study, this treatment approach was effective and safe in routine clinical practice.[5]

Thus, the present study aimed to analyze participant data from the OPTIMISE study conducted at National Cheng Kung University Hospital (NCKUH) in Tainan, Taiwan and determine the difference in the treatment effect between NCKUH data and global data.

Materials and Methods

Study design

This prospective, observational, open-label study was conducted at NCKUH in Tainan, Taiwan. The patient enrollment was conducted between April 2014 and June 2016. The study adhered to the approved protocol, including any amendments, and complied with all relevant health authority requirements and laws. The ethics committees of NCKUH reviewed and approved the study's protocol and any modifications. Before study participation, all patients provided written informed consent.

Study participants

Patients who had histologically proven colon or rectal adenocarcinoma with distal metastasis and had KRAS wild-type status were recruited. These eligible participants were prescribed a first-line combination treatment of cetuximab and a 5-FU-based chemotherapy regimen. Patients who had previously received other target combination chemotherapy were excluded from the study. In addition, patients must have evaluableo or assessable disease at the beginning of the study for response evaluation.

The decisions made by the investigators to exclude patients from the study were in line with the approved label for cetuximab in the first-line treatment of mCRC at NCKUH.

Treatment and follow up protocol

All patients received cetuximab-based 5-FU regimens as per the approved label for cetuximab at NCKUH. Data were collected from the clinical records and other electronic medical records of the patients, such as laboratory and imaging data. The data collection period extended from the time of mCRC diagnosis until the patient's expiration, refusal of treatment, or loss of follow-up until the study ended.

Patients underwent assessments every 4 weeks, which included general evaluation, laboratory investigations, and monitoring for adverse events (AEs). Baseline mutation testing encompassed KRAS and NRAS (not needed in every patient). To determine the tumor status, radiological assessments were performed every 8-12 weeks, following routine practice.

The study participants were followed up to assess survival outcomes for a minimum of 3 years after treatment initiation.

Outcomes

The primary outcome of this study was the overall response rate (ORR), which was defined as the pro-

portion of patients who achieved the best overall response to therapy, measured as either a complete response (CR) or a partial response (PR).

Secondary outcomes comprised progression-free survival (PFS) and overall survival (OS). In addition, we assessed the conversion rate of unresectable tumors to resectable ones was also assessed.

As for safety and toxicity evaluation, secondary endpoints encompassed drug exposure and monitoring of adverse events (AEs).

Statistical analysis

PFS was defined as the duration from the first administration of cetuximab until disease progression (PD, months) or death from any cause. On the contrary, OS was defined as the time in months from the initial treatment to the date of death.

To visualize PFS and OS data, Kaplan-Meier survival curves were constructed.

For safety analyses, the safety population was employed,, including all patients who received at least one or any part of one dose of cetuximab. This population was considered for all safety assessments and analyses.

Results

Patients' general data

Between April 2014 and June 2016, a total of 28 patients who met the selection criteria were enrolled in the OPTIM1SE trial at NCKUH. The mean age of the study participants was 57.9 years, and the majority were male (n = 16, 57.1%). At the beginning of the trial, 3 participants (10.7%) were underweight, 5 (17.9%) were overweight, and none were obese.

Most patients had left-sided tumors (96.4%), with 11 (39.3%) at the rectum; 11 (39.3%), sigmoid colon; 2 (7.1%), rectosigmoid junction; and 3 (10.7%), descending colon. Only 1 (3.6%) patient had a right-sided tumor at the cecum. Liver metastases were the most common metastatic site (n = 21, 75.0%), followed by the lung (n = 4, 14.3%) and peritoneum (n = 4, 14.3%).

Among them, 14 (50%) patients completed the treatment course, and the remaining 14 (50%) discontinued their participation in the study. During the 3-year follow-up period, 17 (60.7%) patients died, and mCRC progression was the primary cause of death for 15 (53.6%) patients. Among the 14 patients who discontinued their participation, reasons included loss of follow-up after the first dose of cetuximab (n = 1, 7.1%), Dengue fever infection (n = 1, 7.1%), patient refusal (n = 3, 21.4%), and others due to ongoing disease progression under treatment.

Pathological reports of all 28 patients confirmed adenocarcinoma, and the majority were moderately differentiated (n = 23, 81.5%). The baseline CEA levels (ng/mL) were categorized as follows: < 5 (n = 7, 25%), 5-20 (n = 9, 32.1%), and > 20 (n = 12, 42.9%) (Table 1).

Table 1. Patient's general data (at NCKUH/Global)

Characteristic	Patient, n (%) (N = 28)/(N = 520)
Age (years)	
Mean	57.9/58.5
Male:female	16:12/318:202
Base line BMI (kg/m^2)	
Underweight (< 18.5)	3 (10.7%)
Ideal (18.5-24.9)	20 (71.4%)
Overweight (25-29.9)	5 (17.9%)
Obesity (≥ 30)	0 (0%)
Primary site of CRC	28 (100)
Rectum	11 (39.3%)/202 (30.8%)
Sigmoid colon	11 (39.3%)/158 (30.4%)
Rectosigmoid junction	2 (7.1%)/53 (10.2%)
Descending colon	3 (10.7%)/32 (6.2%)
Cecum	1 (3.6%)/17 (3.3%)
Metastatic location	
Liver	21 (75%)/338 (65%)
Lung	4 (14.3%)/125 (24%)
Bone	2 (7.1%)/22 (4.2%)
Brain	1 (3.6%)/5 (1%)
Lymph nodes	2 (7.1%)/183 (35.2%)
Peritoneum	4 (14.3%)
Pathology	
Adenocarcinoma	28 (100%)
Well differentiated	2 (7.1%)
Moderately differentiated	23 (81.5%)
Moderately to poorly differentiated	1 (3.6%)
Poorly differentiated	2 (7.1%)
Base line CEA (ng/ml)	
< 5	7 (25%)
5-20	9 (32.1%)
> 20	12 (42.9%)

Primary outcome

This study included a total of 28 patients. The ORR observed was 64.3%, with 16 (57.1%) patients showing a PR and 2 (7.1%) achieving a CR. Among all 28 patients, 28.6% (n = 8) had the best response of PD (Table 2).

Secondary outcomes

As of June 2019, the closure date of the OPTIM1SE study, 25 (89.3%) patients experienced an event during the study, i.e., PD, recurrence or death. Of the 28 patients, 19 (67.9%) died during the study, and 9 (32.1%) were still alive and their status was censored at their last assessment. The median PFS for these 28 patients was 12 (95% CI, 8-26) months (Fig. 1), and the median OS was 28 (95% CI, 16-45) months (Fig. 2).

During the follow-up period, 12 out of the 28 patients underwent metastatic tumor resection. Among these patients, 4 were initially deemed unresectable but later had a resectable status after receiving cetuximab-based 5-FU regimens (Fig. 3).

Safety and AEs

During the study, the majority of patients (78.6% [22/28]) experienced at least one AE. Among the AEs reported, severe malaise, poor intake, and nausea were

Table 2. Best overall response and overall response rate (at NCKUH/Global)

Response	Patient, n (%) (N = 28)/(N = 520)
Best overall response	
Responders	18 (64.3)/236 (45.4%)
Complete response	2 (7.1)/26 (5%)
Partial response	16 (57.1)/210 (40.4%)
No responders	10 (42.9)/284 (54.6)
Stable disease	0 (0)/128 (24.6)
Progressive disease	8 (28.6)/59 (11.3)
Not evaluable	1 (3.6)[†]/17 (3.3%)
Missiing	1 (3.6)/80 (15.4%)
Overall response rate, n (%)	18 (64.3)/236 (45.4%)

[†] The not evaluable one was Dengue fever infection one.

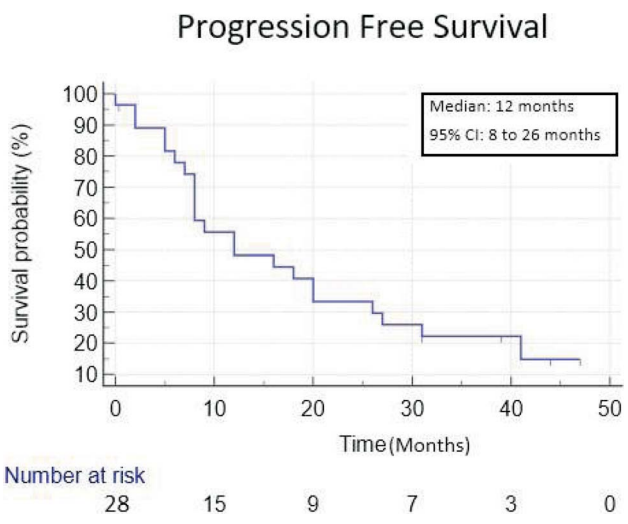

Fig. 1. Kaplan-Meier survival curves. Progression-free survival (PFS).

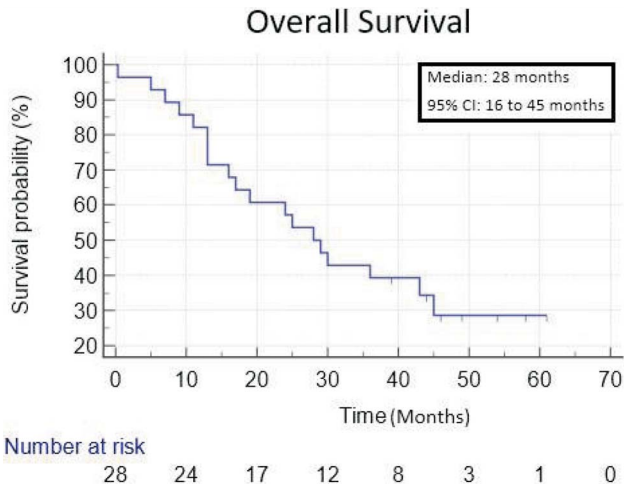

Fig. 2. Kaplan-Meier survival curves. Overall survival (OS).

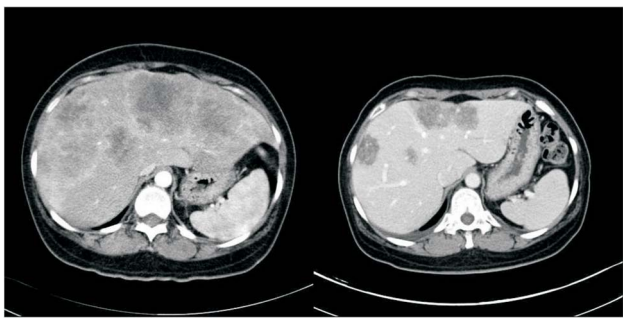

Fig. 3. Before (left) and after (right) cetuximab-based infusional 5-FU regimens treatment CT image of liver metastasis.

the most common reasons for treatment discontinuation, affecting four patients.

The most frequently observed AEs were skin rash (n = 20, 71.4%), fatigue (n = 18, 64.3%) and nausea (n = 12, 42.9%). All the reported AEs were of grades 1-2, indicating mild to moderate severity, and none of the patients experienced severe AEs leading to death.

Overall, the safety profile of the cetuximab-based 5-FU regimens in this study was generally manageable, with no reported cases of severe AEs resulting in fatalities.

Discussion

The TAILOR phase III study was the first clinical trial to prospectively demonstrate the efficacy and safety of combining FOLFOX with cetuximab as a first-line treatment for RAS wild-type mCRC and it provided evidence supporting the use of this combination therapy in patients with RAS wild-type mCRC.[6]

The CRYSTAL study also investigated the use of cetuximab in combination FOLFIRI as a first-line treatment option for mCRC and it showed that adding cetuximab with FOLFIRI, compared with using FOLFIRI alone, reduced the risk of disease progression in patients with mCRC.[7]

The OPTIM1SE study, which included patients from the Asia-Pacific, Middle East, and Russia, revealed that using cetuximab-based 5-FU regimens as the routine first-line treatment for mCRC was effective and safe in real-world practice. The study reported an ORR of 45.4% and a median OS of 30.8 months in these regions.[5]

The participants of the OPTIM1SE study at NCKUH, Taiwan, demonstrated a higher ORR of 64.3% and a median OS of 28 months. The disparity between the mean and median of OS (32.7 vs. 28 months) was due to many patients succumbing early and being unable to complete the treatment.

The complete trial treatment rate in this study was 50% (14/28), which was better than 25% (130/520) in the OPTIM1SE study. When comparing the complete group with the incomplete group, the median of OS was 43.5 months vs. 16.5 months, and the mean OS was 39.4 and 18.6 months, respectively. These results demonstrated that completing trial treatment is crucial for extending the survival time.

Of all 28 patients, 12 (42.9%) patients received metastatic tumor resection, which was higher than the OPTIM1SE study (91/520, 17.5%). Four of them were unresectable initially and became resectable after cetuximab-based 5-FU regimens (the metastatic tumor resection rate increased from 28.6% to 42.9%). According to BELIEF study, the addition of cetuximab to FOLFOX or FOLFIRI significantly increased teh R0 resection rate in initially unresectable mCRC (25.7% vs. 7.4%; $p < .01$).[8] In the CRYSTAL study, after combination with cetuximab, the R0 resection rate increased from 6.5% to 16.3%.[7]

Among the 12 patients who underwent metastatic tumor resection, 7 continued to receive cetuximab and the other 5 patients did not. Currently, no evidence supports the continuation of targeted therapy following metastatic lesion resection surgery. Our data showed that continuing cetuximab treatment was associated with similar OS (mean, 40 vs. 40.6 months; median, 45 vs. 39 months), and 4 and 2 patients were still alive in their respective groups.

In addition, 15 of 28 patients were treated by oncologist, whereas the remaining 13 were treated by a colorectal surgeon. The mean OS periods were 29.5 and 28.5 months, with median OS periods of 28 and 29 months, respectively. No significant difference was found between the two groups in terms of chemotherapy with cetuximab-based 5-FU regimen for mCRC.

The OPTIM1SE study demonstrated that the primary tumor location is a predictive factor for survival benefits with the addition of cetuximab to chemotherapy in patients with RAS wild-type status. In this study, the hazard ratio (HR) for OS favored left-sided over right-sided tumors (HR, 0.69 [95% CI, 0.49-0.99]; $p = 0.042$). This indicates that patients with left-sided tumors experienced better survival outcomes than those with right-sided tumors when treated with cetuximab-based 5-FU regimens.[5]

Similarly, the PRIME and CRYSTAL studies found that left-sided tumors had a survival benefit when treated with cetuximab. In the PRIME study, the HR for OS in left-sided tumors was 0.69 (95% CI, 0.58-

0.83; $p < 0.0001$), indicating a significant survival advantage. Coversely, for right-sided tumors in the PRIME study, the HR for OS was 0.96 (95% CI, 0.68-1.35; $p = 0.802$), suggesting no significant survival benefit with cetuximab treatment.[9] A similar pattern was observed in the CRYSTAL study, further supporting the notion that left-sided tumors derive greater benefit from cetuximab therapy than right-sided tumors.[7]

However, in our study, only one patient had right-sided tumors, which limits the ability to draw definitive conclusions regarding the survival benefit for this subgroup. Nonetheless, the findings of the OPTIM1SE study and other global trials consistently indicate that the primary tumor location plays a significant role in predicting the efficacy of cetuximab-based treatment in patients with RAS wild-type mCRC, with left-sided tumors showing better treatment outcomes.

Moreover, these regional variations and healthcare factors must be considered when interpreting the results of clinical studies conducted in different countries. The effect of insurance restrictions or other healthcare-related factors on treatment outcomes should be carefully evaluated to better understand the effectiveness of specific therapies in different patient populations. As with any real-world study, confounding factors may influence the results, and cautious interpretation of the data is necessary to draw meaningful conclusions.

The combined evidence from the OPTIM1SE study and other global trials supports the efficacy and safety of cetuximab-based 5-FU regimens as a first-line treatment option for patients with KRAS wild-type status mCRC. The improved response rates and OS observed in these studies provide valuable insights for clinical decision-making and can contribute to optimizing treatment strategies for patients with this type of CRC.

Limitations

This study has several limitations that should be acknowledged. First, the small number of patients at NCKUH, Taiwan, may limit the generalizability of the findings to a broader population. A larger sample size would provide more robust and representative results.

Second, the study didn't consider the patient's B-RAF status. Although according to the current NCCN guide line, the patient's B-RAF status was needed to determine whether cetuximab is suitable for treatment, during the enrollment period of the OPTIM1SE trial, this examination was not routine and was not included in the trial's eligibility criteria.

Third, the study's real-world nature introduces inherent limitations, such as potential biases and confounding factors. Data quality and reporting can be influenced by various factors, including differences in medical record documentation, reporting practices, and patient adherence to treatment protocols. These issues could affect the accuracy and completeness of data, leading to potential inaccuracies or missing information.

Conclusion

Overall, the results from the OPTIM1SE study and our analysis at NCKUH, Taiwan, contribute to more evidence supporting the use of cetuximab-based 5-FU chemotherapy regimens as a first-line treatment option for patients with RAS wild-type mCRC. Besides, our data showed higher ORR, complete trial treatment rate, and received metastatic tumor resection rate compared to the OPTIM1SE study. These findings have implications for treatment decisions and highlight the potential benefits of this therapeutic approach in real-world clinical practice. However, the limitations of real-world studies must be considered and results must be cautiously interpreted. Further research, including larger prospective studies, is warranted to confirm and extend these findings.

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原　著

抗 EGFR 標靶藥作為未變異型 K-RAS 患者的第一線治療：OPTIM1SE 試驗於國立成功大學附設醫院之分析

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目的　本研究旨在分析在臺灣臺南國立成功大學醫院 (NCKUH) 進行的 OPTIM1SE 研究的參與者，並確定 NCKUH 數據與全球數據之間的治療效果差異。

方法　這是一項前瞻性、觀察性、開放性的研究，於臺灣臺南國立成功大學醫院 (NCKUH) 進行。參與者為在 2014 年 4 月至 2016 年 6 月期間具有未經治療的組織學證實的結腸或直腸腺癌，並且具有未變異型 KRAS，且至少在 3 年內有追蹤資料的病例。研究的主要結果是整體反應率 (ORR)。次要結果包括無進展生存期 (PFS) 和整體生存期 (OS)。同時也測量了無法切除的腫瘤轉變為可切除腫瘤的轉化率。

結果　在國立成功大學附設醫院 (NCKUH) 的 OPTIM1SE 試驗中，共有符合標準的 28 名患者被納入研究。整體反應率 (ORR) 為 64.3%，其中有 16 名患者 (57.1%) 顯示部分反應，2 名 (7.1%) 達到完全反應。這 28 名患者的中位無進展生存期 (PFS) 為 12 個月 (95% CI 8-26)，中位整體生存期 (OS) 為 28 個月 (95% CI 16-45)。在這 28 名患者中，有 12 名接受了轉移性腫瘤切除手術，4 名最初無法切除，但在接受基於爾必得舒的 5-FU 化療方案後後來變得可切除。總的來說，基於爾必得舒的 5-FU 化療方案的安全性通常是可控的，並且沒有致命的情況發生。

結論　OPTIM1SE 研究的結果以及我們在國立成功大學附設醫院 (NCKUH) 的分析，為基於爾必得舒的 5-FU 化療方案作為未變異型 KRAS 轉移性結腸直腸癌患者的一線治療選擇，提供更多證據。

關鍵詞　5-fluorouracil、爾必得舒、第一線、轉移性結直腸癌、不可切除可切除轉變率、國立成功大學附設醫院、台南、台灣。