TAS-102 Independent and Combined Therapy in Metastatic Colorectal Cancer

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Research Article

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Abstract

Objective
To evaluate the effectiveness and safety of TAS-102 in the treatment of metastatic colorectal cancer.

Methods

The pubmed, web of science, medline, cochrane library databases were searched for the literature on TAS-102 treatment of metastatic colorectal cancer. Extract data such as median Overall Survival (mOS), median Progression-Free Survival (mPFS) and the incidence of adverse events for meta-analysis.

Results

Our study found that the mOS of patients treated with TAS-102 was 7.74 (95%CI: 6.09–9.85) and the mPFS was 2.91 (95%CI: 2.38–3.57). The mOS in patients treated by TAS-102 Combined with bevacizumab is 10.41 (95%CI: 8.40–12.89) and the mPFS is 4.35 (95%CI: 3.05–6.20). In the control experiment, the patients’ mOS and mPFS were improved. TAS-102 + B VS. TAS-102 (OR = 0.41, 95% CI: 0.18–0.93; OR = 0.72, 95% CI: 0.63–0.83). TAS-102 VS. Placebo(OR = 0.44, 95% CI: 0.29–0.67; OR = 0.51, 95% CI: 0.42–0.62). The incidence of adverse events in combination with bevacizumab will increase.

Conclusion

TAS-102 single or combined treatment can significantly improve the survival of patients, and drug safety should be considered when formulating a combined treatment plan.

1 Introduction

By 2020, it is estimated that colorectal cancer is the cause of 935,000 cancer-related deaths worldwide, accounting for 9% of all cancer deaths1. In the initial diagnosis, approximately 25% of colorectal cancer patients have concurrent metastatic disease, and more than half of the patients are diagnosed as metastases2,3. Despite advances in the treatment of metastatic CRC (metastatic colorectal cancer), the survival rate is still poor. And the expected survival period without effective drug treatment is about 6 months4–6.

TAS-102 (trifluridine/tipiracil) is an oral anticancer drug containing a thymidine analogue (trifluridine). It is composed of active cytotoxic component FTD and effective thymidine phosphorylase inhibitor TPI hydrochloride. The molar ratio is 1:0.55. FTD is the active cytotoxic component of the drug. TPI can prevent thymidine phosphorylase from rapidly degrading FTD into inactive form7,8. FTD/TPI is established as the third-line treatment for metastatic colorectal cancer. According to the results of the international phase III RE COURSE study, the study reported the significant benefits of FTD/TPI compared with placebo in terms of overall survival (OS), and acceptable security conditions9,10.

The efficacy and safety of FTD/TPI monotherapy in adults with refractory mCRC was first demonstrated in a Japanese phase II trial by Yoshino et al.5 and later in the pivotal phase III RE COURSE trial6. In these two studies, TAS-102 showed good effectiveness, significantly improving overall survival (mOS) and median progression-free survival (mPFS). TAS-102 combined with bevacizumab have a good effectiveness in the treatment of metastatic colorectal cancer, while reducing the incidence of adverse events.

Regorafenib and TAS-102 are both considered as new treatment options for salvage line therapy. A meta-analysis showed similar effectiveness of the two drugs, but the occurrence of adverse events may be different12. The main goal of clinical trials is to establish the effectiveness and safety of the drug in a carefully selected group of patients. However, there are still differences from real-world applications. The actual application of TAS-102 needs more attention. This study conducted a meta-analysis of clinical trials in the practical application of TAS-102, and compared the safety and effectiveness of drugs in controlled trials and uncontrolled trials.

2 Material And Methods

2.1 Search Strategy
PubMed, Medline, Web of Science, Cochrane databases were searched for eligibility publications. The following keywords were used: "metastatic colorectal cancer" AND "TAS-102" OR "FTD/TPI". There is no time limit for searching until the final search date is May 31, 2021. In addition, the reference list of applicable studies was manually checked for inclusion in other articles. Two researchers jointly complete this search process.

2.2 Inclusion and Exclusion

These articles are manually screened for relevance, first by removing duplicate publications, and then checking the abstract if the title is not enough to exclude. If a publication appears to meet the inclusion criteria after reading the abstract, it will be marked for full text inspection. Review the design, intervention methods, and results of the study, and evaluate compliance with the requirements. Animal experiments, reviews, reports, non-refractory colorectal cancer, inappropriate outcome indicators, non-compliant intervention are the main exclusion principles.

2.3 Data Extraction and Quality Assessment

Two researchers independently extracted relevant information from each study: first author, year of publication, demographic characteristics of participants include age, gender, ECOG performance status, (K) RAS status, grouping scheme, sample size, median os, median pfs, HR, the incidence of grade ≥ 3 AEs. We downloaded the full text. If in doubt, ask the original author for help. The NOS scale is used to evaluate the quality of the included controlled trials. The total score is 9 points, and the scores above 5 are included in the meta-analysis. However, for the included one-arm experiment, the first 8 items of the MINORS item were selected for quality evaluation. Each item is 2 points and the total score is 16 points, 10 points or more enter our research.

2.4 Statistical Analysis

Based on the recommendations of the Cochrane collaboration, quantitative synthesis of the indicators included in the study. In meta-analysis, $I^2 > 50\%$ is considered heterogeneous. In the absence of significant heterogeneity, a fixed-effect model is used; otherwise, a random-effect model is used. Performing sensitivity analyze and subgroup analyze for the included studies to find the reason of heterogeneity. Funnel plots were used to detect whether there is a small research effect.

3 Results

3.1 The characteristics of the included studies

855 studies were retrieved. Two investigators were screened and included 26 studies\textsuperscript{4,5,9–11,15–35}. Including 14 controlled experiments and 12 single-arm experiments. The average age of 3780 participants was over 50 years old. The intervention methods are TAS-102 alone or combined with bevacizumab, and the control is (REG)regorafenib or placebo. The search and screening process is described in Fig. 1. All studies included in this study were based on moderate- to high-quality evidence. Table 1 provides a brief description of these 26 studies. In the included studies, the score of the controlled experiment was above 5, and the score of the uncontrolled experiment was above 10. The quality of the literature can support the meta-analysis. The appendix summarizes the literature quality evaluation situation.
| Study               | Age(years) | Sex male/female | ECOG performance status (0 / ≥1) | KRAS status Wild/Mutated | Methods         | Sample     | mOS(months) | mPFS(months) |
|---------------------|------------|----------------|----------------------------------|--------------------------|-----------------|------------|-------------|--------------|
| Mayer et al, 2015   | 63(27–82)  | 326/208        | 301/233                          | 272/262                  | TAS-102         | 534        | 7.1(6.5–7.8)| 2(1.9–2.1)  |
|                     | 36(27–82)  | 165/101        | 147/119                          | 131/135                  | Placebo         | 266        | 5.3(4.6–6.0)| 1.7(1.7–1.8) |
| Pfeiffer et al, 2020| NA         | NA             | NA                               | NA                       | TAS-102 + B     | 46         | NA          | 4.6(3.5–6.5) |
|                     | NA         | NA             | NA                               | NA                       | TD-102          | NA         | 2.6(1.6–3.5)|              |
| Sueda et al, 2016   | 66(44–80)  | 10/4           | 1/13                             | 9/5                      | TAS-102         | 14         | 6.3(3.21–9.93)| 2.1(0.92–6.39)|
|                     | 59(37–83)  | 12/11          | 10/13                            | 12/11                    | REG             | 23         | 5.8(3.7–11.7)| 3.0(1.64–4.52)|
| Masuishi et al, 2017| NA         | 30/24          | NA                               | 21/32                    | TAS-102         | 54         | 6.5(5.3–8.3)| 2.1(1.8–3.1) |
|                     | NA         | 90/56          | NA                               | 78/67                    | REG             | 146        | 6.7(5.8–7.6)| 2.1(1.8–2.5) |
| Makiyama et al, 2018| 66(39–82)  | 6/5            | 5/6                              | NA                       | TAS-102 + B     | 11         | Not reach   | 5.8          |
|                     | 69(47–82)  | 20/13          | 11/22                            | NA                       | TAS-102         | 33         | 6.4         | 1.8          |
| Yoshino et al, 2012 | > 20       | NA             | NA                               | NA                       | TAS-102         | 112        | 9.0(7.3–11.3)| NA           |
|                     | > 20       | NA             | NA                               | NA                       | Placebo         | 57         | 6.6(4.9-8.0)| NA           |
| Cutsem et al, 2017  | 60.2(11.86)| 31/33          | 28/36                            | 35/29                    | TAS-102         | 64         | 6.5         | NA           |
|                     | 58.5(11.02)| 18/17          | 13/22                            | 17/18                    | Placebo         | 35         | 4.3         | NA           |
|                     | 61.8(9.98) | 167/104        | 138/133                          | 123/148                  | TAS-102         | 271        | NA          | NA           |
|                     | 62.1(10.42)| 82/50          | 68/64                            | 68/64                    | Placebo         | 132        | NA          | NA           |
|                     | 61.9(10.09)| 113/65         | 128/50                           | 94/84                    | TAS-102         | 178        | 7.8         | NA           |
|                     | 62.1(10.40)| 58/30          | 60/28                            | 40/48                    | Placebo         | 88         | 6.7         | NA           |
| Xu et al, 2017      | 58(26–81)  | 170/101        | 64/207                           | 172/99                   | TAS-102         | 271        | 7.8(7.1–8.8)| NA           |
|                     | 56(24–80)  | 84/51          | 30/105                           | 85/50                    | Placebo         | 135        | 7.1(5.9–8.2)| NA           |
| Longo-Muñoz et al, 2016| 61.5(27–81)| 48/32          | 24/56                            | 35/45                    | TAS-102         | 80         | 6.8         | 2            |
|                     | 62.5(39–78)| 21/11          | 11/21                            | 17/15                    | Placebo         | 32         | 4.6         | 1.7          |
| Moriwaki et al, 2018| 64(29–86)  | 197/130        | 128/199                          | 160/161                  | TAS-102         | 327        | 7.4(6.6–8.3)| NA           |
|                     | 64(31–84)  | 126/97         | 95/128                           | 88/109                   | REG             | 223        | 7.9(6.8–9.2)| NA           |
| Kotani et al, 2019  | 60(23–79)  | 35/25          | 35/25                            | 28/32                    | TAS-102 + B     | 60         | 8.6(6.9–10.3)| 3.7(2.3–5.1) |
|                     | 65(30–80)  | 42/24          | 42/24                            | 30/36                    | TAS-102         | 66         | 8.0(6.7–9.4)| 2.2(1.8–2.6) |
### 3.2 Effectiveness of uncontrolled clinical trials

Pooling the PFS data from 12 uncontrolled clinical trials revealed that the mOS of patients with metastatic colorectal cancer was 8.11 (95% CI: 6.57–10.01). A random effect model was used, $I^2 = 79.7\%$ (Fig. 2). Subgroup analysis showed that the mOS of TAS-102 combined with bevacizumab treatment may be higher. TAS-102 + B: mOS = 10.41 (95%CI: 8.40-12.89), TAS-102: mOS = 7.74 (95%CI: 6.09–9.85). A sensitivity analysis that eliminated studies one by one did not detect abnormalities. The funnel chart and Begg's test (Egger's test) show that there is no publication bias.
Similarly, the mPFS of patients was 3.06 (95% CI: 2.52–3.70). A random effect model was used, \( I^2 = 91.8\% \) (Fig. 3). Subgroup analysis did not find a difference between TAS-102 + B and TAS-102 alone. TAS-102 + B: mPFS = 4.35 (95% CI: 3.05–6.20), TAS-102: mPFS = 2.91 (95% CI: 2.38–3.57). A sensitivity analysis that eliminated studies one by one did not detect abnormalities. The funnel chart and Begg’s test (Egger’s test) show that there is no publication bias.

### 3.3 Effectiveness and safety of controlled clinical trials

16 clinical controlled trials were included. Divided into two designs (TAS-102 + B VS. TAS-102 AND TAS-102 VS. Placebo). Under the first scheme, compared with the control group, the mOS was improved, and the risk ratio of death was 0.41 (95% CI: 0.18–0.93). A random effect model was used, \( I^2 = 73.0\% \) (Fig. 4). Similarly, the mOS death hazard ratio in the second scheme was 0.72 (95% CI: 0.63–0.83). A random effect model was used, \( I^2 = 58.7\% \) (Fig. 4). A sensitivity analysis that eliminated studies one by one did not detect abnormalities. The funnel chart and Begg’s test (Egger’s test) show that there is no publication bias.

Under the first scheme, compared with the control group, the mPFS was improved, and the risk ratio of death was 0.44 (95% CI: 0.29–0.67). A random effect model was used, \( I^2 = 60.9\% \) (Fig. 5). Similarly, the mPFS death hazard ratio in the second scheme was 0.51 (95% CI: 0.42–0.62). A random effect model was used, \( I^2 = 52.8\% \) (Fig. 5). A sensitivity analysis that eliminated studies one by one did not detect abnormalities. The funnel chart and Begg’s test (Egger’s test) show that there is no publication bias.

9 studies showed the incidence of grade \( \geq 3 \) AEs in the experimental group and the control group. Compared with the placebo group, there is no difference in safety under the treatment of TAS-102 alone. \( OR = 3.10 \) (95% CI: 0.88–10.87). Random effects model was used, \( I^2 = 84.7\% \) (Fig. 6). Compared with the application of TAS-102 alone, the combination of bevacizumab may increase the incidence of adverse events. \( OR = 2.19 \) (95% CI: 1.40–3.44). The fixed effects model is applied, \( I^2 = 0.0\% \) (Fig. 6). A sensitivity analysis that eliminated studies one by one did not detect abnormalities. The funnel chart and Begg’s test (Egger’s test) show that there is no publication bias.

### 4 Discussion

Almost 55% of colorectal cancer cases worldwide occur in more developed countries. Its incidence continues to rise in developing countries\(^\text{36}\). As with most cancer types, surgery is the main treatment method. For metastatic cancer, cytotoxic methods, such as neoadjuvant therapy and adjuvant therapy, are used before or after it. The main treatment options include fluoropyrimidine, oxaliplatin, and irinotecan. TAS-102 is an anti-cancer drug that has entered people’s field of vision in recent years. Because of its excellent clinical efficacy and safety, it is often added to the treatment of colorectal cancer, gastric cancer in the middle and late stages and anti-cancer treatment programs for metastatic tumors.

Our study found that the mOS of patients treated with TAS-102 was 7.74 (95% CI: 6.09–9.85) and the mPFS was 2.91 (95% CI: 2.38–3.57). The mOS in patients treated by TAS-102 combined with bevacizumab is 10.41 (95% CI: 8.40–12.89) and the mPFS is 4.35 (95% CI: 3.05–6.20). Combination therapy may have better effectiveness. As the current targeted drug for the treatment of metastatic colorectal cancer, it is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), which plays an anti-tumor effect by blocking the formation of tumor blood vessels and regulating the immune function of patients\(^\text{37}\). In 2004, the FDA approved bevacizumab combined with chemotherapy drugs as the first-line treatment for mCRC. A study showed that bevacizumab combined with first-line chemotherapy for metastatic colorectal cancer can significantly prolong the survival and PFS of patients with mCRC, improve the quality of life, increase the resectable rate of metastases, and improve the survival outcome of patients with mCRC\(^\text{38,39}\). The number of adverse events has also been significantly reduced.

Although uncontrolled trials can observe the survival of patients, they cannot specify the improvement in survival. We included 16 studies that included two controlled protocols (TAS-102 + B VS. TAS-102 AND TAS-102 VS. Placebo). In either scenario, we found a significant increase in mOS and mPFS. Surprisingly, we found that TAS-102 combined with bevacizumab will increase the incidence of grade \( \geq 3 \) AEs (\( OR = 2.19, 95\% CI: 1.40–3.44 \)) compared to TAS-102 alone. The safety of bevacizumab is worthy of further consideration. This indicates that clinicians need to make careful decisions when making treatment options for patients with metastatic colorectal cancer, considering the patient’s tolerance to anticancer drugs.

It is necessary to optimize the design plan when evaluating the efficacy of new drugs. Randomized controlled trials such as resource and TERRA are conducted in homogeneous populations, which can minimize the risk of bias\(^\text{40}\). In the current study, we have included real observational studies aimed at evaluating the effectiveness of a relatively small homogeneous population. These studies have the shortcomings of non-randomized controlled studies. The studies we included included controlled and uncontrolled experiments. And the demographic characteristics and disease manifestations of the participants in the experiment are also quite different. This will actually
affect the accuracy of our final results. Therefore, more rigorous and appropriate randomized controlled experiments need to be proposed. The published meta-analysis of TAS-102 involves comparison of the effectiveness and safety of multiple therapeutic drugs. Regorafenib, TAS-102, fruquintinib, panitumumab and cetuximab are recommended single-agent chemotherapy regimens for patients exhibiting disease progression. The safety of these drugs is difficult to assess. But the safety of the drug does affect the confidence of patients in the treatment plan. The most important thing is the improvement of symptoms and the management of side effects.

In a retrospective study, potential predictive or prognostic biomarkers for the efficacy of regorafenib were evaluated. The results indicate that the mutation status of KRAS and PIK3CA may be a predictor of the clinical benefit of regorafenib treatment. However, no biomarkers have been found to predict the efficacy and safety of TAS-102. The frequency of KRAS mutations should be worth exploring, because mOS and mPFS are independent of KRAS status in resource and TERRA, but are highly dependent on KRAS mutations in the second phase of trials in Japan.

Although this study gives the survival status of TAS-102 as a single treatment, it is worth looking forward to the application of the drug combination program may further improve the efficacy of FTD/TPI, and some clinical trials are currently underway.

Declarations

Disclosure:

Approval of the research protocol: N/A

Informed Consent: N/A

Registry and the Registration No. of the study/Trial: N/A

Animal Studies: N/A

Conflict of Interest: N/A

Conflict of interest statement:

The authors have declared that no conflict of interest exists.

Author Contributions Statement:

Cheng-Jiang Liu and Ting Hu wrote the main manuscript text, Ping Shao prepared the tables, Wu-Yang Chu and Yu Cao prepared the figures and Feng Zhang reviewed, revised and polished the article.

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Figure 1

Flow Diagram Showing the Search and Screening Process
Figure 2

mOS in Patients with Metastatic Colorectal Cancer Treated with TAS-102
Figure 3

mPFS in Patients with Metastatic Colorectal Cancer Treated with TAS-102
Figure 4

The Odds Ratio of mOS under TAS-102 Combination and Monotherapy
Figure 5
The Odds Ratio of mPFS under TAS-102 Combination and Monotherapy
Figure 6

The Odds Ratio of Incidence of Grade $\geq$ 3 AEs under TAS-102 Combination and Monotherapy

Supplementary Files

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