TAS-102 an Emerging Oral Fluoropyrimidine

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Abstract. Colon cancer is a common type of cancer with high mortality. The standard therapy for colon cancer is 5-FU-based regimen, although the current response rate to 5-FU is only 10-15%. Various approaches have been used to improve the efficacy of 5-FU including inhibition of its degradation enzyme dihydropyrimidine dehydrogenase (DPD) such as S1, UTF, use of 5-FU pro-drug capecitabine to exploit thymidine phosphorylase (TP) and supplementation of reduced folate acid to increase cytotoxicity. TAS-102 is a newly-developed anti-folate drug containing the 5-FU analogue trifluridine (TFD) and tipiracil hydrochloride (TPI). TPI is an inhibitor of TFD degradation enzyme thymidine phosphorylase and thus increases the bioavailability of TFD. In the present review, we summarize recent progress with regard to TAS-102, including pre-clinical tests and clinical trials. We further propose several approaches to further improve the efficacy of TAS-102 including combination with targeted therapy and immune therapy.

Colorectal cancer is the third most common cancer type in men and the second most common in women worldwide, and is responsible for a large proportion of cancer-related deaths (1). The current therapeutic approach is not satisfactory. The main therapeutic anticancer drug used for colon cancer is 5-fluorouracil (5-FU) (2). 5-FU is an analogue of pyrimidine, which can interfere with DNA and RNA synthesis and inhibit thymidylate synthase (TS) (3). However, the response rate to 5-FU is only 10-15%. Several strategies have been adopted to improve the efficacy of 5-FU including inhibition of its degradation enzyme dihydropyrimidine dehydrogenase (DPD), use of 5-FU prodrug capecitabine (Xeloda) (Roche; Genetech, San Francisco, CA, USA) to exploit thymidine phosphorylase (TP) and supplement reduced folate acid to increase cytotoxicity. In addition, 5-FU has been combined with other chemotherapeutic drugs including leucovorin and oxaliplatin or irinotecan (4). Although the regimen has an extended median survival to 30 months, drug resistance has been a major problem. Drug resistance is usually caused by blocking apoptosis, increased drug metabolism, drug target alterations and decreased ability to repair DNA damage (3, 5). Activation of survival signaling pathways such as the PI3K/Akt pathway reduces the apoptosis caused by chemotherapeutic drugs (6, 7). In vitro experiments showed that activation of the PI3K/Akt pathway by insulin reduced efficacy of 5-FU while inhibition of the pathway increased cytotoxic effects of these drugs on colon cancer cells (8). Akt activation increased the levels of the protein called X-linked inhibitor of apoptosis protein (XIAP) to decrease apoptosis (9, 10). EGFR signaling pathway inhibitor bevacizumab or cetuximab has also been included in the regimen and shown to increase treatment efficacy (11-13).

The initial agent used for inhibition of DPD is uracil that is a natural substrate of DPD and can thus prevent 5-FU breakdown by competition (14). UFT consists of Ft (tegafur) (Merck Serono, Korea United and Taiho, mostly in Asia, Europe, South America, Central America and South Africa) combined with uracil in a 1:4 molar ratio. It was shown to show greater efficacy than Ft alone. Later, a more potent DPD inhibitor CDHP (5-chloro-2,4-dihydroxypyridine) was developed, whose efficacy is 200-fold that of uracil. This led to development of S1 that includes Ft, CDHP and OXO (potassium oxonate) at molar ratio of 1:0.4:1.0). OXO can reduce gastrointestinal side-effects (15, 16).
TAS-102 is a new formula developed by Taiho Oncology (Taiho Pharmaceutical Co., Ltd. Japan) that contains trifluridine (TFD), an analogue of 5-FU and tipiracil hydrochloride (TPI), an inhibitor of TFD degradation enzyme thymidine phosphorylase (17). TAS-102 has been shown to significantly increase treatment efficacy. TAS-102 has been approved in Japan for refractory colorectal cancer and Taiho Oncology has launched application in USA. In the present review, we summarise most recent progress with regard to use of TAS-102 with emphasis in clinical trials and propose several approaches to further improve the efficacy of TAS-102.

Rationale

Chemically, TFD is a nucleotide analogue (5-trifluoromethyl-2'-deoxyuridine) that can be incorporated into DNA, inhibiting DNA synthesis (Figure 1) (18). It also inhibits TS, which is necessary for the synthesis of deoxynucleotides. Decreased deoxynucleotides prevent DNA synthesis.

TFD is administered orally due to prolonged toxicity caused by i.v. injection (19). TFD is phosphorylated by thymidine kinase (TK) to TF-TMP, TF-TDP and TF-TTP. TF-TTP incorporated into DNA and cause DNA damage and cell deaths. TFD is catalyzed by thymidine phosphorylase (TP) into its inactive form.

TFD is rapidly degraded to its inactive form by TP, thus its efficacy is limited by its low bioavailability (20). TPI was invented to increase TFD bioavailability (21, 22). TPI can inhibit TP and thus increase the bioavailability of TFD. Different ratios of TFD to TPI have been tested and experiments showed that the ratio for the mixture at 1:0.5 reached the optimal efficacy (21, 22).

Pre-clinical Data

Single-agent studies. Both in vitro cell culture systems and in vivo animal experiments have been used to test the efficacy and toxicity of TAS-102 as well as the mechanisms of anti-tumor effects of TAS-102. The effectiveness of TAS-102 has been demonstrated in several xenograft mouse models (23-25). Tanaka et al. showed that TAS-102 increased median survival time of KM20C xenograft mice from 38 days to 70 days. The mechanism is due to FTD incorporation into DNA rather than inhibition of TS. Although both FTD and fluorodeoxyuridine (FdUrd) inhibited TS, washout experiments showed that the effect of FTD on TS was rapid while that of FdUrd persisted. The anti-tumor effect of TAS-102 is explained by decreased proliferation indicated by decreased Ki-67 and increased apoptosis indicated by observed swollen nuclei.

A recent study showed that TAS-102 caused hematological toxicity in a dose-dependent manner and this was in correlation with increased cytotoxicity to cancer cells (26). TFD can be also incorporated into blood cells and be the cause of side-effects. These side-effects limit the dosage of TAS-102 used clinically. Overcoming such side-effects will markedly increase treatment efficacy.

Combination Studies

In an animal model, TAS-102 has been tested in combination with irinotecan hydrochloride and showed promising results (27). In colorectal and gastric cancer xenograft-bearing nude mouse models (by KM12C, KM12C/5-FU, DLD-1/5-FU, and SC-2 cells respectively), combination of TAS-102 (orally administered twice a day from day 1 to 14), and irinotecan hydrochloride (administered intravenously on days 1 and 8) showed superior effect of tumor growth-inhibitory activity and RTV5 (period required to reach a tumor volume that was five-times greater than the initial volume) to TAS-102 or irinotecan hydrochloride as monotherapy.

Anti-EGFR antibodies bevacizumab, cetuximab and panitumumab have been shown to increase the efficacy of TAS-102 in a xenograft colon cancer mouse model (28). In a xenograft colorectal cancer model, the efficacy of TAS-102 was improved by combining it with bevacizumab, cetuximab or panitumumab. Combination use of TAS-102 (orally administered twice a day from day 1 to 14), and bevacizumab (administered intraperitoneally twice a week for 2 weeks) had a greater effect on tumor growth inhibition and longer RTV5 than those with TAS-102 or bevacizumab alone in the SW48 and HCT116 tumor models (28). It has also been revealed that the addition of anti-EGFR antibody increased the concentration of phosphorylated FTD in tumors compared to TAS-102 alone. There exist no clinical trials for combination therapy with TAS-102 and anti-EGFR antibodies.

Clinical Studies

Phase I. Phase I studies have been undertaken in both Japan and USA. In a phase I study, 21 Japanese patients were recruited for a dose escalation study from 30 to 70 mg/m² per day (29). TAS-102 was administered orally twice daily on days 1-5 and 8-12 in a 28-day cycle. The treatment reached 50% disease control and median progression-free survival of 2.4 months. The side-effect is neutropenia grade 4 in a dose-dependent fashion. Two out of 21 patients had side-effects. In a USA study, Hong et al. tested TAS-102 in 14 patients and found that 50 mg/m²/day were tolerated (30). Several other phase I studies have been also performed, showing promising outcomes (31-33).

Hong et al. studied the pharmacokinetics of TAS-102 using repeating treatment course of oral administration once daily for 14 days followed by 7 days of rest (30). The initial dosage used was 100 mg/m²/day, that caused severe side-
effects of grade 3 or 4 in course 1 in two out of 14 patients. Therefore, the dosage was adjusted to 50 mg/m\(^2\)/day, in which no side-effect occurred and this dosage was identified as dose-limiting toxicity, as elevation of dosage to 60 mg/m\(^2\)/day resulted in severe side-effects. FTD’s \(T_{\text{max}}\) was identified to be 0.506-1.33 h. \(T_{1/2}\) was 1.37-1.55 h. Approximately 1.0% to 16.7% of FTD in urine was not metabolized.

In a phase I combination study for TAS-102 and irinotecan, 7 patients were treated with 50 mg/m\(^2\)/day of TAS-102 plus 150 mg/m\(^2\) irinotecan and 3 patients treated with 60 mg/m\(^2\)/day of TAS-102 plus 150 mg/m\(^2\) irinotecan (34). The later regimen showed severe side-effects including neutropenia, leukopenia, lymphopenia and anaemia. In terms of efficacy, 2 patients had partial responses. The pharmacokinetics of TAS-102 are not affected by irinotecan. Although the recommendation dose was identified as 50 mg/m\(^2\) plus 150 mg/m\(^2\) irinotecan, further studies with much higher number of patients are required. Doi et al. tried another dose for TAS-102 in a phase I study (29). It used 35 mg/m\(^2\) twice daily for 5 days and had 2 days for rest. This was then followed by another cycle then 14 days of rest. This approach increased the dosage to be used but not inducing severe adverse effects.

**Phase II.** Based on phase I studies, a phase II clinical trial was undertaken, performed in Japan with 169 colorectal cancer patients being recruited. The selected patients had a history with treatment of 2 or 3 regimens of chemotherapy and became resistant to fluoropyrimidine, irinotecan and oxaliplatin (35). The median survival was reported to be 9.0 months compared to 6.6 months in the placebo group. It has been reported that approximately 50% of patients (57 out of 113) had a side-effect of neutropenia at grade 3 or 4 while leucopenia and anaemia accounting for 20% and 17%.

**Phase III.** Recently, a phase III clinical trial was conducted and its results were reported (36). The double-blind trial was carried-out in multi-centres worldwide. As many as 800 patients were recruited. These patients were randomly selected for the TAS-102 treatment or for placebo. The patients were treated with TAS-102 at a dosage of 35 mg/m\(^2\) or placebo twice daily for 5 days followed by 2 days of rest. This was repeated once followed by 2 weeks of rest. The results showed that median overall survival increased from 5.3 months to 7.1 months (36). The side-effects included neutropenia (38%), leukopenia (21%), febrile neutropenia (4%). Although survival time was only extended by 2 months, the result is very promising (37, 38).

**Ongoing Studies**

At present, 12 clinical trials for TAS-102 are ongoing (https://clinicaltrials.gov/ct2/results?term=TAS-102). TAS-102 will be tested for solid tumors including metastatic colorectal cancer. It will also be tested in various conditions including hepatic and renal impairment as well as resistance to standard chemotherapy. Future studies should include combination of TAS-102 with inhibitors or antibodies used for targeted therapy.

**Toxicities and Differences from S-1, Xeloda and UFT**

The toxicity of TAS-102 is mild that can be solved by reducing dosage or short disruption. The main adverse effect of TAS-102 is bone marrow suppression. A study showed that neutropenia caused 22% patients to have one dose reduction while 31% patients to have a treatment interruption (35). Grade 3 or 4 neutropenia occurred in 50% of patients treated with TAS-102. Other haematological adverse effects included leucopenia (28%), anaemia (17%), lymphopenia (10%) and thrombocytopenia (4%). Non-haematological adverse effects were also found in low frequencies including fatigue (6%), diarrhea (6%), nausea (4%), anorexia (4%), febrile neutropenia (4%) and vomiting (4%). No grade 3 or 4 hand-foot syndrome and peripheral neuropathy were found. Hand-foot syndrome is a common adverse effect of xeloda. It was reported that xeloda caused 18.1% of this syndrome. Another adverse effect of xeloda was diarrhea, that occurred in 15.4 of patients (39).
Discussion

Although TAS-102 has been shown to increase median survival rate by 2 months in the phase III clinical trial, further improvement of treatment efficacy is necessary for cancer patients. Several approaches are likely to increase TAS-102 efficacy dramatically including combination use with targeted therapy agents, combination with immunotherapy and nano-delivery of TAS-102 or TAS-102-based combination therapeutic agents.

Although the activation of signaling pathway has not been studied for drug resistance to TAS-102, activation of many signaling pathways has been shown to decrease the effects of 5-FU (3, 41). PI3K/Akt pathway is well-known to play key roles in carcinogenesis, metastasis and drug resistance in many cancers including colorectal cancer (42-47). Therefore, inhibition of the pathway has been extensively tested for treatment of cancer (48, 49). Activation of the PI3K/Akt has been shown to increase drug resistance in colon cancer cell lines and inhibition of that pathway increased the sensitivity of colon cancer cells to 5-FU and other chemotherapeutic agents (6, 8, 50). Activation of NF-kB pathway is also well-known to cause drug resistance to chemotherapeutic agents in cancer treatment (51, 52). In view of the important role of EGFR in colorectal cancer, antibodies against EGFR have been used clinically, a fact taken place in combination with 5-FU (53-55). The roles of these pathways in treatment efficacy of TAS-102 could be studied and thus combination therapy of TAS-102 with targeted therapy can be developed.

TAS-102 may be used together with immunotherapy in colorectal cancer. It is now realized that immune responses play key roles in anticancer treatment. Activated T-cells can kill cancer cells directly. However, cancer cells including colorectal cancer cells have developed an immune escape ability through increased expression of inhibitory molecules such as programmed death-ligand 1 (PD-L1) (56, 57). PD-L1 binds to programmed death-1 (PD-1) on T-cells, leading to T-cell dysfunction and apoptosis (58, 59). Anti-PD-L1/PD-1 antibodies have been developed to inhibit PD-L1/PD-1 to activate T-cells, showing effectiveness in a proportion of patients in clinical trials (60-62). Therefore, it is possible to combine TAS-102 with anti-PD-L1 or PD-1 antibody to further improve the efficacy of TAS-102.

Conclusion

TAS, although only by two months, has significantly increased median survival time. The mechanism lies in DNA synthesis damage rather than TS inhibition. Further improvement may include combination use with signaling molecule inhibitors and anti-PD-L1/PD-1 antibodies.

References

33 Green M, Pusztai L, Theriault R, Adinin R, Hofweber M, Fukushima M, Mita A, Bindra N and Hortobagyi GN: Phase I study to determine the safety of oral administration of TAS-102 on a twice daily (BID) schedule for five days a week (wk) followed by two days rest for two wks, every (Q) four wks in patients (pts) with metastatic breast cancer (MBC). ASCO Annual Meeting Proceedings; 2006.