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Two-Nucleoside Combination In Solid-Tumors: TAS-102 Provides Clear Benefits For The Cancer Patients.

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ABSTRACT

TAS-102 is a new combination of trifluridine and tipiracil that is effective in the therapy of some solid tumors. Trifluridine induces DNA fragmentation as it is incorporated the DNA molecules. Its anticancer activity takes place even after oral administration. Tipiracil is a nucleoside analog with a sugar moiety replaced by a modified pyrolidine system. Tipiracil prevents trifluridine conversion to an inactive metabolite. The mechanism of this trifluridine protection is based on the inhibition of thymidine phosphorylase and, consequently, on increasing trifluridine bioavailability. Tipiracil also acts as a platelet-derived endothelial cell growth factor and provides an indirect antiangiogenic effect that is also beneficial in cancer therapy of solid tumors]. Trifluridine – tipiracil combination currently used mainly in patients with refractory and metastatic colorectal cancer under the name TAS-102 consists of both substances in the molar ratio 1:0.5. During the year 2017, FDA, USA published the Approval summary for TAS-102 produced as Lonsurf by Taiho Oncology, Inc. for the therapy of metastatic colorectal cancer following the use of fluoropyrimidine, oxaliplatin, and irinotecan, an anti-VEGF (human epidermal growth factor) biological therapy and an anti-EGFR (human epidermal growth factor receptor) therapy. The published data clarified that TAS-102 is active in human cell resistant to 5-fluorouracil. This seems to be important as it may be successful as a chemotherapeutic agent after 5-fluorouracil therapy. On the other hand, it was also shown that cell resistant to TAS-102 component, trifluridine, due to the absence of functional thymidine kinase remain sensitive to 5-FU, and 5-FU metabolism and cytotoxicity are not modified in this case. Recent clinical investigations recommend combining TAS-102 with oxaliplatin (TAS-102: 35 mg/m^2 on days 1-5 and 15-19; oxaliplatin: 85 mg/m^2 on days 1 and 15 every 4 weeks). Other combinations of TAS-102 are under investigation.

Keywords: Trifluridine; tipiracil; thymidine phosphorylase; TAS-102; colorectal cancer;

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INTRODUCTION

Nucleosides, and after their phosphorylation – nucleotides, represent basic components of DNA and RNA structure. Consequently, inhibition or interference with nucleoside metabolism in cancer cells plays a significant role in the therapy of various malignancies. TAS-102 is a new combination of trifluridine (FTD) and tipiracil hydrochloride (TPI) (Fig. 1 A,B) suitable for oral administration. TAS-102 is shown to be effective in the therapy of some solid tumors. The goal of this article is to review available information on TAS-102.

TRIFLURIDINE (FTD) - 2'-DEOXY-5-TRIFLUOROMETHYLURIDINE

FTD is a thymidine derivative - 2'-deoxy-5-trifluoromethyluridine. It can also be named trifluorothymidine and abbreviated as TFT. This derivative was prepared by replacing 3 hydrogens in the thymidine methyl group (at the pyrimidine ring) by 3 atoms of fluorine (Fig. 2A).

Chemical properties of FTD are similar to other nucleosides. Its molecular formula is $C_{10}H_{11}F_3N_2O_5$ of molecular weight 296.2 g/mol. FTD IUPAC names is: 1-[(2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-(trifluoromethyl)pyrimidine-2,4-dione indicating the presence of 3 centers of optical activity. FTD is water soluble, hydrophilic, with log P -0.7 [1].

The mechanism of action of FTD as an antiviral agent has is not completely clear. FTD seems to inhibit viral replication, and also it gets incorporated into viral DNA during replication. This results in leads to the formation of defective proteins and an increased occurrence of mutations. The same mechanisms are in place for FTD anticancer effects. When FTD enters the cell, it is phosphorylated by thymidine kinase to the FTD monophosphate and subsequently to FTD triphosphate. FTD triphosphate is easily incorporated into the DNA of tumor cells instead of thymidine. This compromises DNA functions, DNA synthesis, and cellular proliferation. The degradation processes of FTD triphosphate are significant and their prevention was always thought to increase FTD biological activity [2,3]. Moreover, FTD monophosphate also inhibits thymidylate synthetase that is required for DNA synthesis [4,5]. Concentrations of this enzyme are increased in various cancer cells and this may even lead to the resistance to nucleoside-based anticancer therapy [4]. FTD is only moderately cross-resistant to 5-FU [4].

FDT possesses its anticancer activity due to induction of DNA fragmentation after it is incorporated (as a triphosphate) into DNA molecules [6]. Investigations of FTD anticancer activity revealed that its anticancer activity takes place even after oral administration. Despite FTD lipophilicity, this is due to various transporters, such as concentrative nucleoside transporter (CNT) 1 present in small intestinal epithelial cells, and possibly also due to the action of equilibrative nucleoside transporters 1 and 2 (ENT 1 and 2) [7]. The involvement of CNT1 was proved in rat cells by the experiments showing the FTD uptake inhibition by thymidine that serves as a CNT1 substrate [6].

FTD was shown to be incorporated in the DNA more than fluorouracil (5FU), and, because of this, FTD cytotoxic effect may differ from the effect of 5FU [8]. Incorporation of FTD into the DNA of HeLa cells is approximately 300-times higher compared to 5FU and 8-times higher compared to 5-fluorodeoxyuridine [8]. No detectable excision of FTD incorporated into DNA and paired with adenine or thymine was observed, but the pairings to guanine were excisable [8]. However, it was shown that resistance to FTD may occur due to decreased thymidine kinase and ENT expression or due to the increase in concentrations secretory phospholipase A2 or due to other mechanisms [9].

Originally, FTD was used as an anti-viral, specifically anti-herpes agent in ophthalmology. It was approved for medical use in 1980 [10]. It is similar to 5-iodouridine or just iodouridine (iodoxuridine) in this aspect (Fig. 2B) [11]. The main indications for the use of FTD are primary keratoconjunctivitis and recurrent epithelial keratitis caused by herpes infection. FTD is active against both types of Herpes simplex virus - type 1 and 2 [10].

TIPIRACIL HYDROCHLORIDE (TPI) - A THYMIDINE PHOSPHORYLASE INHIBITOR

Tipiracil - TPI – is chemically 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]-1*H*-pyrimidine-2,4-dione (Fig. 2B). TPI is a nucleoside analog with a sugar moiety replaced by a pyrolidine system with a modified substitution

of =N-H instead of hydroxyl (-OH) substituent. As other hydroxyls of the sugar moiety are removed, this is technically not a nucleoside but only an analog. The nucleoside base has a chlorine substituent at the position 5 making it an analog of 5-fluorouracil - 5FU. The molecular formula of TPI is $C_9H_{11}ClN_4O_2$ and molecular weight of TPI is 242.663 g/mol. It possesses satisfactory water solubility of 5mg/ml (when heated) [12].

The main therapeutic use o TPI is in preventing FTD conversion to an inactive metabolite 5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione. The mechanism of this FTD protection is based on the inhibition of thymidine phosphorylase (TP). Consequently, FTD bioavailability is increased. Additionally, TP as platelet-derived endothelial cell growth factor and inhibition of its activity results in an indirect antiangiogenic effect (also beneficial in cancer therapy of solid tumors) [12]. TPI is excreted in the feces (49.7%) and the urine (27%). TPI excreted from urine is mainly unchanged (79.1%). Half of the TPI excreted in the feces is also not metabolized. The only TPI metabolite detected is 6-hydroxymethyluracil (6-HMU). Binding to plasma proteins is also low, 8% [13].

TAS-102: TRIFLURIDINE - TIPIRACIL COMBINATION IN CANCER THERAPY

Trifluridine – tipiracil (FTD - TPI) combination currently used mainly in patients with refractory and metastatic colorectal cancer under the name TAS-102 consists of both substances in the molar ratio 1:0.5 [14]. Reports on the first clinical trials are reported by Japanese investigators in 2004 [14-16]. Two mechanisms of activity were reported for this drug. Both mechanisms are related to the metabolism of thymidine. One is the inhibition of thymidylate synthase (TS) and the second one – incorporation of FTD into DNA [14]. This second mechanism is associated with thymidine kinase (TK) and thymidine phosphorylase (TP) activities in a tumor [14]. FTD is structurally an isoster of 5-FU. However, no relationship between the growth inhibition of malignant cells was observed between FTD and 5-FU [15]. Additionally, TAS-102 was shown to possess anticancer activity in 5-FU-resistant human cancer cell lines. The mechanism of activity in these cells is based on FTD incorporation in DNA structure [16], especially when the cancer cells are in the environment containing FTD for a short period of time. Anticancer activity of FTD can be then observed based on the induction of DNA fragmentation that appears after FTD incorporation into the DNA structure [16].

In 2006, Phase I of TAS-102 study was performed in the order to determine the safety and pharmacokinetics of oral TAS-102 in patients with solid tumors. The goal of this phase was to establish the maximum tolerated dose, dose-limiting toxicities, pharmacokinetic profile, and recommended Phase II dose of oral administration of TAS-102 [17]. Administration of TAS-102 was oral dose once daily during 14 days and then a 1-week rest. This was repeated every 3 weeks. The initial dose of TAS-102 was 100 mg/m2/day. However, the first 2 patients experienced substantial toxicity (bone marrow suppression. This led to the use of decreased doses of 50 mg/m2/day of TAS-102 in subsequent patients that were in the following therapeutic course increased to 60 mg/m2/day. At the end of this Phase I study, 50 mg/m2/day was declared the maximum tolerated dose for this therapeutic regime and this dose was recommended for Phase II of TAS-102 investigation [17].

During Phase I investigations, some other regimes of TAS-102 were investigated. These regimes were once/day on days 1-5 and 8-12 every 4 weeks or once/day on days 1-5 every 3 weeks [18]. In total, 63 patients were administered 172 courses of therapy. The maximum tolerated dose varied among patients from 70 mg/m^2/day to 110 mg/m^2/day in the first regime and between 120 mg/m^2/day and 180 mg/m^2/day in the second regime. The dose limited toxicity was observed in the form of granulocytopenia in the vast majority of patients. Other side non-dose limiting effects were nausea, fatigue, granulocytopenia, anemia, diarrhea, and abdominal pain. However, no objective effects were observed in 5-FU-resistant patients. Based on these results, doses recommended for Phase II of TAS-102 clinical investigations were 100 mg/m^2/day for the first regime and 160 mg/m^2/day for the second regime [18]. When the first regime was modified to administer the daily dose three times per day, granulocytopenia remained the main toxicity. The 5-FU refractory disease did not respond but some patients experienced prolonged stable disease [19]. Similar results obtained in Japanese patients with solid tumors refractory to standard chemotherapy were published in 2012 [20]. TAS-102 was given two times/day on days 1-5 and 8-12 in a 28-day cycle The dose was not above 70 mg/m^2/day because of the risk of grade 3 and 4 neutropenia [20]. However, it was concluded in 2012 that TAS-102 possesses 'promising efficacy and a manageable safety profile in patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapies' [21]. In 2015, combinations of TAS-102 and irinotecan on human cancer xenografts were investigated [22] and, additionally, Phase I of clinical investigation of this combination was evaluated in

Japan in patients with advanced colorectal cancer [23]. In general, at this time, TAS-102 was clearly accepted to be beneficial in patients with refractory colorectal cancer as it significantly improved the overall survival of these patients [24,25] and demonstrated an acceptable safety profile [26,27], including cardiac safety as the drug did not demonstrate any effect related to cardiac repolarization [28].

Recently in 2016, results of EPOC1201 study (a multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer) were published [29]. It was shown during the Phase III investigations that TAS-102 at the dose of 35 mg/m^2 gave a clinical improvement in patients with gastric cancer. Additionally, in the same year, the suitability of TAS-102 for patients with cardiac issues, both preexisting or 5FU therapy-related, was shown [30]. This is very important as cardiac side effects are relatively common in fluoropyrimidine therapeutics. The different mechanism of activity may explain with this observation [30]. As more patients received TAS-102 as part of their treatment, it was observed that neutropenia indicated better prognosis in treated refractory metastatic colorectal cancer subjects [31]. Also, it was recommended that, after a proper investigation, to increase the dose of TAS-102 in patients without neutropenia to induce it as neutropenia seems to be a predictor of overall TAS-102-treated patients' survival [31,32]. On the other hand, frequent gastrointestinal toxicities affect TAS-102-related adherence to therapeutic plans. This represents a problem as TAS-102 is administered orally [33,34].

An attempt to use TAS-102 in the second-line therapy of lung cancer was not successful as the Phase 2 study was terminated due to the absence of better TAS-102-related therapeutic outcomes compared to topotecan or amrubicin that serves as comparators [35].

Further investigations of TAS-102 determined in 2017 that despite its similar efficacy compared to regorafenib, different toxicity profiles of these two third-line drugs may be used to select the more suitable one for an individual patient [36] while taking into consideration two-time higher cost-effectiveness of TAS-102 therapy compared to regorafenib [37]. The selection of one of these two drugs for therapy may benefit a patient but a predictive biomarker was not determined yet [38]. Therapeutic outcomes with regorafenib seem to be improved in patients under 65 years of age but TAS-102 seems to work better in older patients [38].

The year 2017, Food and Drug Administration (FDA, USA) published the Approval summary [39] for TAS-102 produced as Lonsurf by Taiho Oncology, Inc. for the therapy of metastatic colorectal cancer following the use of fluoropyrimidine, oxaliplatin, and irinotecan, an anti-VEGF (human epidermal growth factor) biological therapy and an anti-EGFR (human epidermal growth factor receptor) therapy. Additionally, at this time, results of Phase 1/2 performed in Japan were published [40] on combining TAS-102 and bevacizumab with the conclusion that this may be introduced as a treatment option for refractory metastatic colorectal cancer.

The published data [41] clarified that TAS-102 is still active in human cell resistant to 5-FU. This seems to be important as it may be successful as a chemotherapeutic agent after 5-FU therapy. On the other hand, it was also shown that cell resistant to TAS-102 component, trifluridine, due to the absence of functional thymidine kinase remain sensitive to 5-FU, and 5-FU metabolism and cytotoxicity are not modified in this case [42].

The most recent pharmacological studies of TAS-102 concentrated on additional aspects affecting its use. It is now clear that TAS-102 should not be used in patients suffering from moderate/severe hepatic impairment [43]. On the other hand, it may be used in patients over 75 years of age [44]. Also, recent clinical investigations recommend combining TAS-102 with oxaliplatin (TAS-102: 35 mg/m^2 on days 1-5 and 15-19; oxaliplatin: 85 mg/m^2 on days 1 and 15 every 4 weeks) [45]. Other combinations of TAS-102 are also under investigation.

The most recent works still concentrate on indicators/predictors of TAS-102 therapy success TAS-102 being recommended as a salvage therapy for metastatic colorectal cancer. It was shown that the pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are negatively but significantly associated with progression-free and overall survival values and that this is of a significant prognostic value [46]. However, these are data from only 33 patients.

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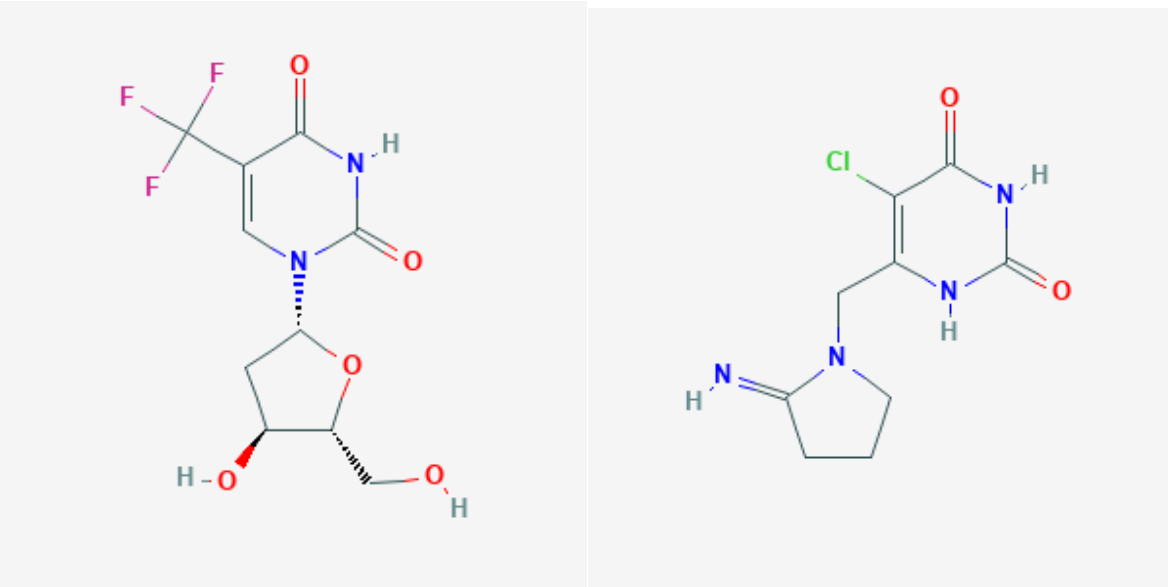
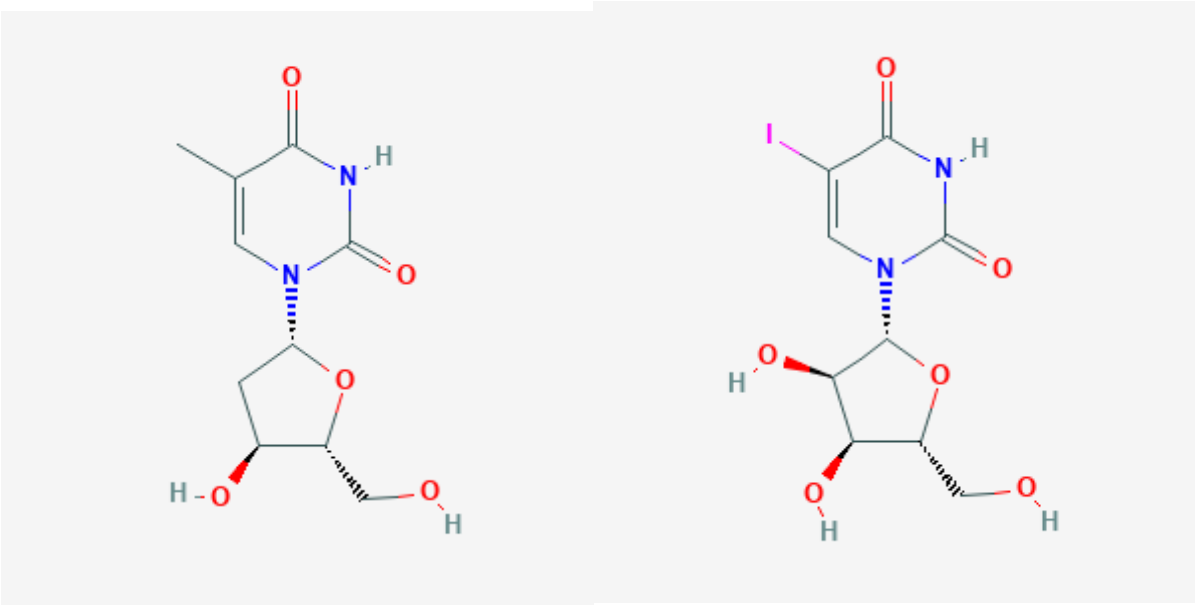
Fig. 1. Chemical structure of TAS-102 components.

A) Trifluridine; 2'-Deoxy-5-trifluoromethyluridine
B) Tipiracil; 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]-1*H*-pyrimidine-2,4-dione



A **B**

Fig. 2. The chemical formula of a naturally occurring nucleoside thymidine (A) and iodouridine (|B).



A **B**

CONCLUSIONS

TAS-102 as a newer addition to chemotherapeutic anticancer agents represents a successful addition to therapy of refractory or resistant-to-therapy metastatic colorectal cancer. However, it shows that even after many years of investigating various nucleoside-based anticancer agents, our understanding of the area may still be improved. This is illustrated by the following: 1) TAS-102 is not a single agent as it is a combination of two substances (FTD and TPI in the molar ratio 1:0.5). This combination improves anticancer activity, brings better therapeutic outcomes, and at the end, it benefits cancer patients. 2) FTD as a fluorine-containing nucleoside would be expected to act similarly to 5-FU. However, there are significant differences in their mode of action and these two substances are not cross-resistant. Also, there are age-related differences in the response to TAS-

102 that need to be addressed in future as varying activities of enzymes over the patient's lifespan, during the progression of the disease, and also due to the applications of various anticancer therapies change.

The findings regarding TAS-102 clearly indicate that many improvements of cancer treatments can be expected in the area of anticancer chemotherapy even after these many years of its investigations and applications to patients.

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