Article published online: 2024-02-05



Gastrointestinal Cancers

# Practical Consensus Guidelines for the Use of S-1 in GI Malignancies

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South Asian J Cancer 2024;13(1):77–82.

## Abstract

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S-1 (5-fluorouracil prodrug [tegafur] in combination with 5-chloro-2,4-dihydroxypyridine [CDHP] and potassium oxonate [OXO]) was first approved in 1999. In order to make it easy for community oncologists, we decided to put together this expert consensus guideline for its use in gastrointestinal (GI) malignancies. A total of 15 subject matter experts used modified Delphi method to discuss, analyze, and vote on key aspects regarding practical approach to use of S-1 in GI cancers, a process involving 6 months of work. The consensus guidelines specify how S-1 use can be optimized in patients with colorectal, gastric, and pancreatic tumors. The voting for the 17 key points resulted in a majority consensus for all the statements (approval ranging from 13/15 [87%] to 15/15 [100%]). S-1 is a combination of three drugs (tegafur, CDHP, and OXO) specifically designed to reduce toxicity and enhance efficacy; clinical data and meta-analysis confirm both factors; and it is recommended as standard of care for GI cancers. S-1 is approved and one of the standards of care for all lines of therapy in colorectal cancer and pancreatic cancers. S-1 with oxaliplatin is the standard of care for gastric cancers.

**Keywords**

- SCOPE-C
- IASCO
- Tegafur
- OXO
- CDHP
- SAARC

DOI https://doi.org/10.1055/s-0043-1778685 ISSN 2278-330X

**How to cite this article:** Parikh PM, Sahoo TP, Biswas G, et al. Practical Consensus Guidelines for the Use of S-1 in GI Malignancies. South Asian J Cancer 2024;13(1):77–82.



Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

## Introduction

That 5-fluorouracil (5-FU) is a chemotherapeutic agent useful in a wide range of solid malignancies is well established fact. It is especially invaluable in gastrointestinal (GI), head neck, and breast cancers. Keeping in mind the limitations and challenges of infusional 5-FU, efforts were focused to develop an oral fluoropyrimidine.[1] Oral 5-FU is rapidly metabolized in the gut wall because of the presence of high levels of dihydropyrimidine dehydrogenase (DPD). This drastically reduces absorbed and circulating levels of the active drug. The first step was the utility of a prodrug (tegafur). It was then combined with CDHP (5-chloro-2,4-dihydroxypyridine; gimeracil), a competitive inhibitor of DPD that prevents degradation of 5-FU. To the mix was also added OXO [potassium oxonate] that inhibits phosphorylation of 5-FU and therefore it reduces serious GI toxicities like nausea, vomiting, stomatitis, and diarrhea; it is especially important for the Caucasian population.[2] This led to the successful invention of S-1 (5-FU prodrug [tegafur] in combination with CDHP and OXO.[3] As an oral drug, S-1 is conveniently administered and problems associated with infusional administration are averted (e.g., central venous access-associated infection, thrombosis, and bleeding). We, therefore, decided to put together the rationale, current evidence, and expert consensus guidelines for the use of S-1 in GI malignancies.

## Methods

We invited subject matter experts with real-world experience to become part of our committee. This included 15 oncologists who were recognized thoughtful leaders in the field of GI malignancies and who had a track record of dealing with day-to-day management of GI cancer (all the coauthors). They represented the full spectrum of academic oncology centers, government, and private hospitals, as well as oncology societies across India. Their combined experience represented management of a large volume of GI cancers. We followed the modified Delphi method to conduct a series of interviews first.[4] This was followed by discussions within the group. The discussion points were analyzed, and feedback provided to expert faculty. Then an in-person meeting of the expert committee was held under the banner of IASCO (Integrated Academic Society of Clinical Oncology), and voting was conducted to finalize the development of these Practical Consensus Guidelines for the use of S-1 in GI malignancies. This took into consideration published evidence combined with the real-world practical experience of our national and international experts.[5] The voting using Delphi method was repeated thrice, each time the experts being given the voting results along with additional publications and data relevant to the questions being discussed. Over a period of six months, the experts arrived at the final version of this practical consensus guidelines statement for the benefit of our oncology colleagues, providing ready-to-use practical guidelines.

## Results and Practical Consensus Guideline Recommendations

The expert group was cognizant of the Globocan data which documented that the incidence of GI Cancers was 23.4% and their mortality was 35.6 %.[6,7] Also published literature showed that, in India, almost one-fourth of gastric cancers present with metastatic disease at initial presentation and it is the second most common cause of death due to cancer in the adult population.[8,9] In addition, the incidence of colorectal cancer (CRC) was increasing exponentially after the age of 60 years and hence it now constitutes a major component of geriatric oncology.[10,11] Older patients are at higher risk of toxicity for a number of reasons, including mobility limitations, comorbidities, poly pharmacy, cognitive impairment to name a few.[12] Due to cultural and social differences, Indian older cancer patients and those from other low- and middle-income countries (LMIC) are best evaluated by using screening tools developed and validated locally.[13–15] Since sociocultural features are similar among South Asian Association for Regional Countries (SAARC) countries, the SCOPE-C Ver2 questionnaire is recommended as the ideal screening tool for older patients with cancer in SAARC.[16]

### Colorectal Cancer

S-1 has been studied extensively, received first approval in Japan in 1999, approved by European Marketing Agency (EMEA) in 2011 and is currently approved in 30 countries (including India) for seven indications.[17,18] For CRC, it is approved for all indications namely first-line metastatic, second-line metastatic and adjuvant settings—based on data from international trials like SOX-COX, SOFT, TRICOLORE, SALTO, NORDIC9, BASIC, FIRIS, and ACTS CC02 studies.[19–25] Based on the NORDIC9 and BASIC data, it has been shown that S-1 alone or in combination with oxaliplatin is safe and convenient schedule for the elderly patients with metastatic CRC.[26,27] This also led to the incorporation of S-1 in pan Asian European Society of Medical Oncology (ESMO) consensus guidelines.[28]

### Gastric Cancer

For gastric cancer, data from 13 trials and two meta-analysis shows that S-1 based chemotherapy gives results identical to that with capecitabine-based chemotherapy, albeit with lesser side effects.[29,30] This S-1 combination is safer than capecitabine combinations.[30] In fact, Lee et al have shown that S-1 monotherapy gives results similar to the CAPOX combination when used as adjuvant therapy in gastric cancer.[31] This is also true in the geriatric population.[32]

Combination of S-1 with oxaliplatin (SOX) has been studied in detail because it has the benefit of overcoming drug resistance in tumors that express high DPD.[33] Since SOX and CS (cisplatin with S-1) give identical results, SOX should replace CS in the management of chemotherapy-naïve patients with advanced gastric cancer (because of its favorable safety profile).[34] The ARTIST II study has also shown that for node-positive gastric cancer after D2 resection, adjuvant therapy with SOX or S-1 plus RT is superior to S-1 alone.[20]

 

### Pancreatic Cancer

As far as pancreatic cancer (PC) is concerned, the JASPAC-01 phase III study identified S-1 as the new standard adjuvant treatment for resected PC.[35] In fact, the Japanese clinical practice guidelines recommend S-1 as one of the standard Rx options for all lines of treatment of PC in the neo-adjuvant, adjuvant, locally advanced, and metastatic settings.[36] This will solve the current problem that older patients of PC are often denied the benefit of CT, in both the palliative and adjuvant treatments, thereby reducing their OS.[37,38]

The expert group thus arrived at the practical consensus guidelines for the use of S-1 in GI malignancies as shown in ►Table 1.

**Table 1** Practical consensus recommendation guideline—Delphi voting by IASCO Expert Committee

| Sr no | | Agree | Disagree | Abstain |
|---|---|---|---|---|
| 1 | Global incidence of GI malignancies is 23.4 % and their mortality is 35.6 % | 14 | 1 | 0 |
| 2 | In India, one-fourth of patients with gastric cancer present with metastatic disease | 14 | 1 | 0 |
| 3 | Incidence of CRC is increasing faster in the geriatric age group, where it forms a major chunk of geriatric oncology patients | 14 | 1 | 0 |
| 4 | Patients from India, SAARC region, and other LMIC are best screened by using a tool invented, evaluated, and validated (SCOPE-C) within our social and cultural milieu | 14 | 0 | 1 |
| 5 | In CRC, S-1 is approved and a good option for all lines of therapy—based on SOX-COX, SOFT, TRICOLORE, SALTO, NORDIC9, BASIC, FIRIS AND ACTS CC02 studies | 13 | 1 | 1 |
| 6 | S-1 monotherapy or in combination with oxaliplatin is a safe and convenient schedule for geriatric metastatic CRC patients | 15 | 0 | 0 |
| 7 | In gastric cancer, S-1 based CT and capecitabine-based CT give similar results for RR, DFS, and OS | 15 | 0 | 0 |
| 8 | S-1-based CT is safer than capecitabine-based CT based on meta-analysis of available data | 14 | 1 | 0 |
| 9 | S-1 monotherapy gives results similar to CAPOX in adjuvant therapy for gastric cancers | 13 | 1 | 1 |
| 10 | In the elderly, S-1 gives better results than CAPOX | 15 | 0 | 0 |
| 11 | SOX combination is able to overcome drug resistance in tumors that express high DPD | 13 | 1 | 1 |
| 12 | SOX gives identical results as CS in advanced gastric cancer | 14 | 0 | 1 |
| 13 | SOX should replace CS in the management of chemotherapy-naive advanced gastric cancer patients because of better safety profile | 14 | 0 | 1 |
| 14 | In gastric cancer, for patients who have undergone D2 resection and are node positive, adjuvant therapy is better with SOX or S-1 plus RT as compared to S-1 monotherapy | 15 | 0 | 0 |
| 15 | In pancreatic cancer, S-1 is the new standard of care in the adjuvant setting | 14 | 0 | 1 |
| 16 | In pancreatic cancer, S-1 is a standard treatment option for all lines of therapy—neoadjuvant, adjuvant, locally advanced, and metastatic settings | 14 | 0 | 1 |
| 17 | In pancreatic cancer, older patients are often unnecessarily denied the benefit of CT, resulting in pooper OS—in the adjuvant and palliative settings | 15 | 0 | 0 |

Abbreviations: CRC, colorectal cancer; CS, cisplatin with S-1; DFS, diffusion-free survival; DPD, dihydropyrimidine dehydrogenase; GI, gastrointestinal; IASCO, Integrated Academic Society of Clinical Oncology; LMIC, low- and middle-income countries; OS, overall survival; SAARC, South Asian Association for Regional Countries; SOX, S-1 plus oxaliplatin.

 

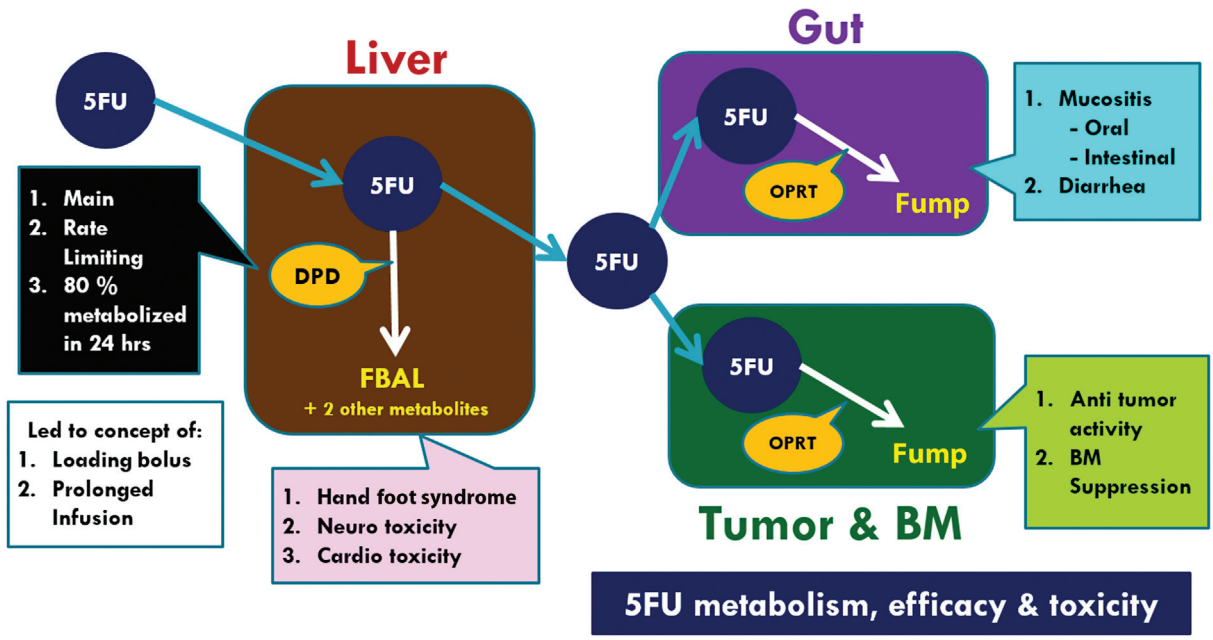


**Fig. 1** 5-fluorouracil (5FU) metabolism, efficacy, and toxicity pathways. BM, bone marrow; DPD, dihydropyrimidine dehydrogenase.

## Discussion

The process for regulatory approval for new medicines varies across the world. Each country focuses on the most important unmet needs of their own population. In oncology, most novel agents are welcomed with enthusiasm, followed by skepticism before the pendulum settles somewhere in-between.

For S-1 it has been different. Having emerged from Asia, it was met by the west with disdain and skepticism. That is why the U.S. Food and Drug Administration (USFDA) is yet to approve this drug.[39,40] Since National Comprehensive Cancer Network (NCCN) guidelines only include drugs that are approved by US FDA, S-1 has been "conveniently" left out. However, the overwhelming evidence gathered from across the globe, including Europe, forced EMEA to approve S-1 in 2011.[18] So the application, data, and approvals for S-1 have been steadily increasing, making it a unique CT drug in which the pendulum is moving only in the positive direction.

What is the reason? Regular 5FU has a highly variable pharmacokinetic profile. This leads to erratic efficacy and toxicity, which are often difficult to predict.[41] The usual metabolic pathway is by degradation in the liver (main and rate limiting enzyme DPD is responsible for 80% degradation within 24 hours) (►Fig. 1). But population studies have shown that DPD levels vary by as much as 37%.[41,42] Conversion of 5FU to FBAL contributes to hand foot syndrome (HFS), neurotoxicity, and cardiotoxicity. The 5FU that escapes degradation in the liver finds its way to the tumor, bone marrow (BM), and gut. In the gut, the enzyme OPRT degrades 5FU to FUMP, which contributes to mucositis and diarrhea. In the tumor and in the BM, conversion to FUMP leads to antitumor activity as well as BM suppression (►Fig. 1). S-1 is a combination of three drugs (tegafur, CDHP, and OXO), designed to reduced toxicity and enhance efficacy.[43] The pro-drug, tegafur, of S-1 enters the liver and CYP2A6 (cytochrome p450 enzyme) converts it into 5FU. In the liver, CDHP blocks DPD and hence the metabolism of 5FU (►Fig. 2). In the absence of metabolites, HFS, neurotoxicity, and cardiotoxicity are reduced. When the 5FU enters the gut, OXO blocks its conversion into FUMP. This reduces the toxicities of mucositis and diarrhea. In the tumor cells (and in the BM), OXO does not enter and hence OPRT is unopposed, leading to unabated FUMP formation. Therefore, the antitumor efficacy remains intact (and so does the BM suppression). This the S-1 triple combination delivers what it is specifically designed to improve efficacy while reducing toxicity.[41–43]

This is good news for patients with GI malignancies—whose incidence is increasing, effective systemic therapy needs improvement and application of emerging approaches has the potential to improve outcome.[3,44–46] For instance, the incidence of DPD/DPYD is sufficiently high in India to factoring that possibility in the decision-making process, while prescribing 5FU or its analogues (including capecitabine & tegafur).[47,48] The higher incidence of HFS among patients being treated with capecitabine also makes S-1 safer and patient friendly.[49] In fact, even if a patient develops toxicity due to 5-FU or capecitabine, data shows that S-1 can still be used with reasonable safety.[50]

## Conclusion

S-1 monotherapy or in combination with other agents is a useful, effective, and safe option in the management of GI malignancies. Failure to use this option in our patients can compromise their outcome and shorten survival. S-1 is especially useful in geriatric oncology. These practical consensus guidelines provide detailed recommendations for the

 

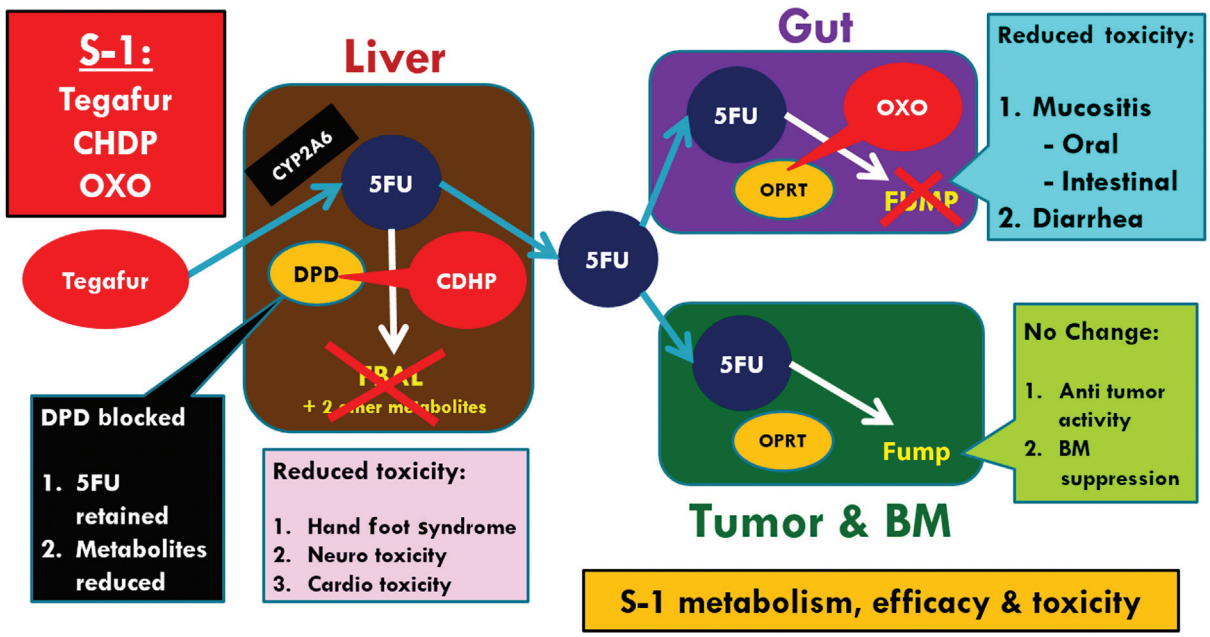


**Fig. 2** S-1 metabolism, efficacy, and toxicity pathways. BM, bone marrow; CDHP, 5-chloro-2,4-dihydroxypyridine; DPD, dihydropyrimidine dehydrogenase; 5FU, 5-fluorouracil.

use of S-1 in GI malignancies, especially in India, SAARC region, and other LMIC. ►Table 1 gives a clear and unambiguous consensus on the use of S-1 in day-to-day practice.

## Conflict of Interest

None declared.

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