

Fluorouracil Bolus Use in Infusional Regimens Among Oncologists—A Survey by Brazilian Group of Gastrointestinal Tumors

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PURPOSE The utility of administering fluorouracil (5-FU) in bolus in regimens of infusional 5-FU has been questioned. We aimed to quantify the use of 5-FU bolus in infusional regimens for gastrointestinal malignancies among Brazilian oncologists.

METHODS This was a cross-sectional electronic survey composed of eight multiple-choice questions sent to Brazilian oncologists during 14 days in February 2021. The survey instrument collected demographic data of participants and assessed practices in terms of 5-FU bolus use. We evaluated the association of demographic variables and 5-FU prescribing patterns with Fisher's exact test (odds ratio [OR]).

RESULTS The survey was completed by 332 medical oncologists. Overall, 37% were experienced oncologists and 32% were gastrointestinal specialists. In the first-line metastatic and in the adjuvant settings, 40% and 67% of oncologists always prescribe 5-FU bolus in infusional regimens, respectively. Experienced oncologists more frequently omit 5-FU bolus when compared with early-career oncologists, both in the metastatic (41% v 26%; OR, 1.98; $P = .005$) and adjuvant settings (28% v 14%; OR, 2.32; $P = .003$). In addition, more GI specialists remove 5-FU bolus when compared with generalists, but only in the metastatic setting (44% v 25%; OR, 2.33; $P = .001$). GI specialists are more likely to consider that treatment efficacy is not affected by 5-FU bolus withdrawal than are generalists (89% v 75%; OR, 2.65; $P = .003$). Most respondents (67%) keep leucovorin at the same doses when omitting 5-FU bolus, and only 16% always recommend dihydropyrimidine dehydrogenase testing.

CONCLUSION Our survey indicates that experience in oncology practice and percentage of time dedicated to treat GI cancers influence the prescription of 5-FU bolus in Brazil, with more frequent omission of it among experienced gastrointestinal specialists, particularly in the metastatic setting.

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INTRODUCTION

Fluorouracil (5-FU), a pyrimidine analogue with anti-metabolite activity, has been widely used in several anticancer regimens since 1957, when its clinical activity was first reported.^{1,2} Most gastrointestinal malignancies have been systemically treated with schemes including 5-FU in their backbone, both in early and late stages.

Although many bolus 5-FU schedules were initially prescribed, current routine practice is characterized by a preference for the modified de Gramont regimen, in which 5-FU is given alone or combined with other chemotherapies and/or monoclonal antibodies. It consists of a 2-hour infusion of leucovorin (LV; 400 mg/m²) followed by a push (ie, bolus) administration of 5-FU (400 mg/m²) on day 1 and then continuous 46-hour infusions of 5-FU (2,400 mg/m²) administered every 14 days.³

The omission of bolus 5-FU in the modified de Gramont regimen has not been directly tested against its use in randomized trials. Nonetheless, retrospective data have pointed toward a better toxicity profile without compromising efficacy.⁴⁻⁶

Although the utility of administering 5-FU in bolus in regimens of infusional 5-FU has been questioned, how often this is practiced by oncologists is unknown. Therefore, we aimed to quantify the use of 5-FU bolus in infusional regimens for GI malignancies among Brazilian oncologists and to investigate oncologists' characteristics associated with the administration of 5-FU bolus.

METHODS

This was a cross-sectional electronic survey performed and sponsored by the Brazilian Gastrointestinal Tumors Group (GTG). It was composed of eight multiple-choice

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CONTEXT

Key Objective

How frequently do oncologists remove fluorouracil (5-FU) bolus in infusional regimens? In the first-line metastatic setting, 40% of oncologists in Brazil always prescribe 5-FU bolus in infusional regimens, as compared with 67% in the adjuvant scenario.

Knowledge Generated

Omission of 5-FU bolus is more frequent among experienced oncologists and those who dedicate more than 50% of their practice to treat gastrointestinal cancers.

Relevance

Given the potential to decrease costs and toxicities, more studies are needed to explore patient- and health care-related factors associated with the use of 5-FU bolus and leucovorin in patients with gastrointestinal cancers and the true efficacy of those drugs in infusional regimens.

questions sent to Brazilian medical oncologists through social media (WhatsApp, Instagram, and Facebook) by the board of directors of GTG during 14 days in February 2021. Each question allowed only one answer by respondent.

The survey instrument collected demographic data of participants and assessed current practices in terms of 5-FU bolus use. Participants with > 10 years in oncology practice were considered experienced (early career otherwise) and those with > 50% of their clinical practice dedicated to treat patients with GI malignancies were deemed specialists (generalists otherwise).

Descriptive statistics were used to summarize the results. We evaluated associations of demographic variables and 5-FU prescribing patterns with Fisher's exact test, reporting respective odds ratios (ORs) of comparisons between groups. Two logistic regression models were performed to evaluate factors associated with 5-FU bolus withdrawal. Independent variables (experienced v young oncologist; GI specialist v generalist oncologist) with $P < .05$ were entered in the multivariable analyses. Final P values $< .05$ were considered significant.

RESULTS

The survey was completed by 332 medical oncologists from across the country. The description of the eight questions with their answers in terms of number and percentages is shown in [Table 1](#).

Overall, 37% were experienced oncologists and 32% were GI specialists. In the first-line metastatic setting, 40% of the oncologists always prescribe 5-FU bolus in infusional regimens, whereas 19% never prescribe it. Meanwhile, in the adjuvant setting, 67% of the respondents always prescribe 5-FU bolus when initiating infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimens and 13% never prescribe it, as shown in [Figure 1](#).

Experienced oncologists more frequently omit 5-FU bolus when compared with early-career oncologists, both in the metastatic (41% v 26%; OR, 1.98; $P = .005$) and adjuvant settings (28% v 14%; OR, 2.32; $P = .003$). In addition,

more GI specialists remove 5-FU bolus when compared with generalists in the metastatic setting (44% v 25%; OR, 2.33; $P = .001$), but not in the adjuvant setting (21% v 19%; OR, 1.17; $P = .66$; [Fig 1](#)).

The most frequent reason to omit 5-FU bolus was toxicity (97%), and most respondents (67%) keep LV at the same doses when omitting 5-FU bolus, whereas 26% of the oncologists remove it. Overall, 80% of the participants consider that removing 5-FU bolus does not compromise effectiveness of infusional 5-FU regimens. GI specialists are more likely to consider that the treatment efficacy is not affected by 5-FU bolus omission than generalist oncologists (89% v 75%; OR, 2.65; $P = .003$).

Most respondents (56%) never test patients for dihydropyrimidine dehydrogenase (DPYD) deficiency before starting capecitabine or 5-FU. Only 16% of oncologists always recommend DPYD testing before prescribing fluoropyrimidines, without differences between GI specialists and generalists or experienced and early-career physicians. Only one oncologist (< 1%) was not aware of the DPYD test.

DISCUSSION

The present survey demonstrates that less than half (40%) of oncologists in Brazil always administer 5-FU bolus when first prescribing FOLFOX or fluorouracil, leucovorin, and irinotecan (FOLFIRI) to patients with metastatic cancer. In the adjuvant setting, 67% of them always prescribe 5-FU bolus when initiating adjuvant FOLFOX. We believe that less oncologists prescribe 5-FU bolus for metastatic disease since the goal of treatment is not cure. At the same time, concerns with toxicity tend to be higher in the metastatic setting. Experienced oncologists and GI specialists were independently more likely to omit 5-FU bolus. To our knowledge, no other study has investigated the rate of 5-FU bolus use in oncology clinical practice.

In gastrointestinal cancers, a variety of dosage schedules of FOLFOX and FOLFIRI have been used over time, with or without a monoclonal antibody. Nowadays, mFOLFOX6, which consists of biweekly oxaliplatin (85 mg/m²), LV

TABLE 1. Description of the Eight Questions and Frequency of Answers

Questions	No. (%)
1. How long have you been practicing medical oncology? (years)	
< 5	110 (33)
5-10	98 (30)
11-20	77 (23)
> 20	47 (14)
2. What percentage of your practice time is dedicated to treat gastrointestinal cancers?	
< 25	95 (29)
25%-49%	129 (39)
50%-75%	64 (19)
> 75%	44 (13)
3. In the treatment of metastatic disease, considering a patient who will start FOLFOX or FOLFIRI in first line, do you use bolus of 5-FU on D1?	
Never	63 (19)
Rarely	42 (13)
Sometimes	93 (28)
Always	134 (40)
4. In the adjuvant setting, considering a patient who will start FOLFOX, do you use 5-FU bolus on D1?	
Never	44 (13)
Rarely	21 (6)
Sometimes	45 (14)
Always	222 (67)
5. What is the main reason for removing 5-FU bolus?	
Reducing costs	2 (1)
Reducing the patient's stay at the clinic or hospital	8 (2)
Reducing toxicity	322 (97)
6. When you remove 5-FU bolus, what do you do with leucovorin (folinic acid)?	
I remove it	86 (26)
I reduce its dose	22 (7)
I keep it at the same dose	224 (67)
7. In terms of effectiveness of FOLFOX and FOLFIRI regimens, do you feel comfortable removing 5-FU bolus?	
No	68 (20)
Yes	264 (80)
8. Do you usually test patients for DYPD deficiency before starting 5-FU or capecitabine?	
Never	185 (56)
I don't know the test	1 (0)
I only recommend it for high-risk groups (eg, elderly)	94 (28)
I always recommend DPYD testing	52 (16)

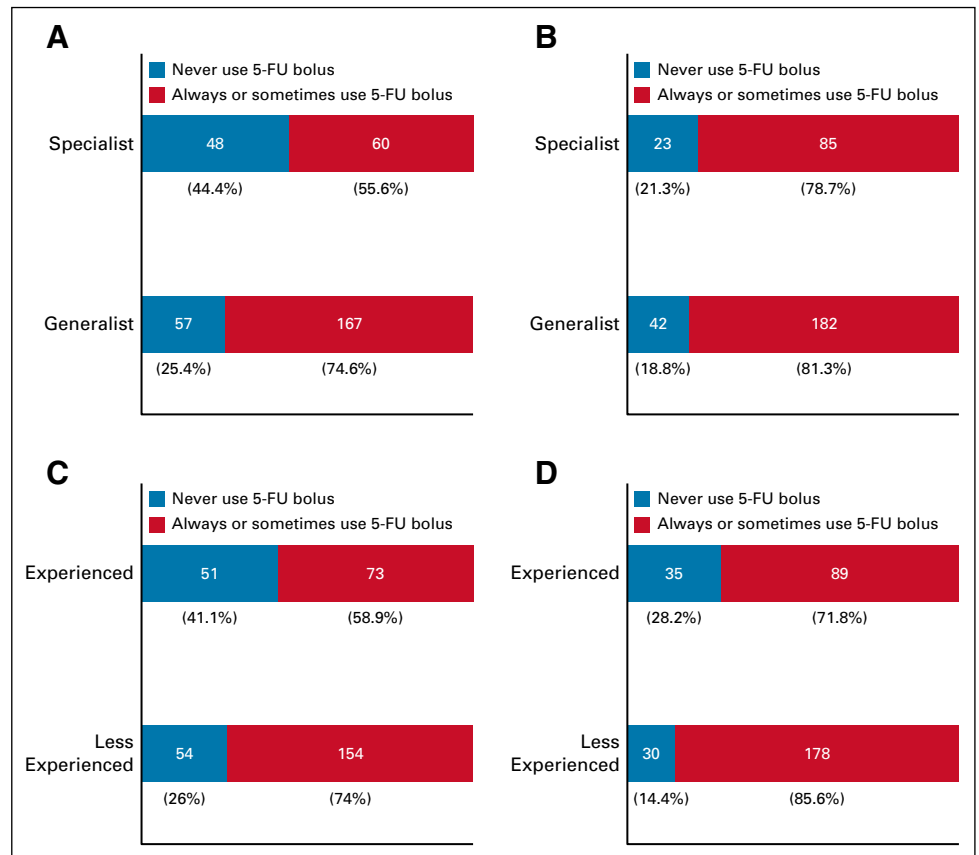
Abbreviations: DPYD, dihydropyrimidine dehydrogenase; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FU, fluorouracil.

(400 mg/m²), and 5-FU (400 mg/m² administered by intravenous bolus, followed by 2,400 mg/m² given as a 46-hour continuous infusion), is the most commonly prescribed regimen, both in clinical practice and in randomized clinical trials. When FOLFIRI is concerned, biweekly irinotecan (180 mg/m²), LV (400 mg/m²), and 5-FU (400 mg/m² administered by intravenous bolus, followed

by 2,400 mg/m² given as a 46-hour continuous infusion) is the usually prescribed regimen.

Whenever a patient develops hematologic toxicity, most oncologists remove 5-FU bolus from the infusional schedules. In parallel, more fragile patients tend to begin doublet regimens without 5-FU bolus to reduce the incidence of toxicities. Over time, many GI specialists

FIG 1. Prescribing patterns of 5-FU bolus in (A and C) metastatic and (B and D) adjuvant settings according to time dedicated to treat gastrointestinal malignancies and years of oncology practice. FU, fluorouracil.



abandoned 5-FU bolus in infusional regimens, despite the absence of comparative trials.

A Japanese retrospective study aimed to compare mFOLFOX6 plus bevacizumab with mFOLFOX7 (without 5-FU bolus) plus bevacizumab in 39 patients with metastatic colorectal cancer to assess the clinical relevance of omitting bolus 5-FU.⁶ Given the better toxicity profile and similar clinical outcomes, the authors raised the question whether bolus 5-FU could definitely be omitted when prescribing FOLFOX. Although the omission of 5-FU bolus has never been directly tested against its use, mFOLFOX7 (without 5-FU bolus) has already been part of some phase III trial arms. In the CONcept trial, which evaluated the role of intermittent oxaliplatin, both arms included mFOLFOX7 with bevacizumab.⁷ In this study, only 2% of the patients developed severe myelosuppression.

More recently, a retrospective study compared clinical outcomes of 133 patients with metastatic colorectal cancer who received mFOLFOX6 with or without 5-FU bolus and LV. The authors found no differences in median progression-free survival (PFS) or overall survival (OS) between the groups. Despite reduced growth factor utilization, the nonbolus group achieved a favorable safety profile with less treatment-related hematologic events.⁴ Another large retrospective study including 252 patients with metastatic colorectal cancer (who received

mFOLFOX6 with or without bolus 5-FU) showed no impact of 5-FU bolus omission on median PFS, or neutropenia. A significantly inferior OS for the group who did not receive bolus 5-FU (median 2.5 v 1.8 years) was observed in the univariable analysis, but this was not confirmed in the model adjusted for tumor sidedness and *performance status*.⁵ Given the retrospective nature of these studies and the fact that oncologists typically omit 5-FU bolus in older and more frail patients, results may have been influenced by these variables.

Interestingly, the majority of the participants consider that omitting 5-FU bolus does not compromise effectiveness of infusional regimens. The question of what to do with LV when omitting 5-FU bolus in infusional regimens should also be further investigated, since LV increases efficacy of 5-FU bolus when this is used alone, but the role in infusional regimens is less clear.⁸ In our survey, besides the 40% of respondents who maintain 5-FU bolus when starting FOLFOX or FOLFIRI, only 26% of the oncologists remove LV when 5-FU bolus is not used. The EORTC 40952 phase III trial with 497 treatment-naïve patients with metastatic colorectal cancer evaluated the impact of LV during a weekly infusional 5-FU regimen on OS. Patients were randomly assigned to one of the three arms: 24-hour infusional 5-FU with or without LV (500 mg/m²) or bolus 5-FU and LV (Mayo Clinic schedule). Median PFS was significantly longer for infusional 5-FU with LV (5.6 months)

versus bolus 5-FU and LV (4.1 months) and infusional 5-FU without LV (4.0 months), with a *P* value of .029. Response rate was also numerically higher, albeit not significantly different, for the addition of LV on infusional 5-FU.⁹ There was no gain in OS, but increased toxicity was observed among those who received infusional 5-FU with LV in comparison with infusional 5-FU alone, with more grade 3 or 4 diarrhea (22% v 6%). Therefore, it seems that omitting 5-FU bolus of infusional 5-FU regimens is harmless, but LV should be maintained—although the optimal dosage is debatable.

Removing 5-FU bolus brings down the costs. Not only the entire regimen will cost less, but it is also expected that fewer patients will require hospitalization. In developing countries, such as ours, this is an even more important matter. We have also found that DPYD testing is low in Brazilian routine practice before fluoropyrimidine initiation, which possibly reflects the costs associated with the test. Deficiency of DPD affects approximately 5% of the global population. In these patients, the lack of enzymatic activity increases the half-life of fluoropyrimidines, resulting in excess drug accumulation and toxicity.¹⁰ It has been recommended that fluoropyrimidines should be omitted or dose-reduced in patients carrying *DPYD* genetic variants conferring an increased risk of toxicity. However, oncology

societies disagree on recommending systematic testing and no Brazilian statement has been made so far.

Our study has some limitations. Because the e-mailing of our survey was not centralized, we did not have the total number of oncologists who received it. Thus, the survey response rate could not be calculated. In addition, because the GTG directors sent the survey to their contacts, the study sample likely reflects oncologists mostly interested in GI cancers. In this regard, the external validity of our study could be conformed in a larger sample since it is possible that our results may be overestimated in terms of 5-FU bolus omission—as generalists tend to maintain 5-FU bolus more often than do GI specialists.

Given the potential to decrease costs and toxicities, more studies are needed to explore patient- and health care-related factors associated with the use of 5-FU bolus and LV in gastrointestinal cancers.

In conclusion, our survey demonstrates that longer experience in oncology practice and higher percentage of time dedicated to treat GI cancers influence the prescription of 5-FU bolus in Brazil, with more frequent omission among experienced oncologists and GI specialists, particularly in the metastatic setting. DPYD testing is very low in routine practice before fluoropyrimidine initiation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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