Is it Time to Forget the 5-Fluorouracil Bolus?

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5-Fluorouracil (5-FU) is an essential component of multiple treatment regimens for gastrointestinal cancers. Since Heidelberger et al[1] first reported that 5-fluoropyrimidines have anticancer efficacy in 1957, many investigations have observed that prolonged-infusion 5-FU is more effective and less toxic compared to 5-FU bolus, especially with regard to myelosuppression.[2] Clinical studies further indicated superior efficacy with 5-FU delivered as continuous infusion compared with bolus dosing.[3] Nevertheless, as a result of the complementary mechanisms of action, bolus 5-FU interfering with RNA synthesis and the continuous infusion affecting DNA synthesis, and differential pharmacokinetics, with the bolus attaining fast maximum plasma concentration and the continuous infusion resulting in sustained exposure and lower clearance,[4] combined 5-FU bolus + continuous infusion was evaluated in clinical trials. In 1997, de Gramont et al[5] demonstrated that 5-FU bolus + leucovorin (folinic acid) followed by continuous infusion conferred superior response rates compared with 5-FU bolus/leucovorin alone in patients with metastatic colorectal cancer (CRC; overall response rate [ORR], 33% vs 14%), albeit with no significant survival benefit (13 months), and established the benchmark for using 5-FU bolus + continuous infusion in future investigations.

Subsequently, multiagent 5-FU–based chemotherapy strategies have been developed to improve upon stagnant survival rates, but randomized clinical studies continued to use almost universally 5-FU bolus + continuous infusion. In the early 2000s, the addition of oxaliplatin to the folinic acid + 5-FU bolus/continuous infusion regimen (FOLFOX)[6] and irinotecan to the folinic acid + 5-FU bolus/continuous infusion regimen (FOLFIRI)[7] increased response rates to 40% to 50% and survival rates to 16 to 17 months.

However, few retrospective and prospective studies compared multiagent FOLFOX or FOLFIRI regimens with and without 5-FU bolus (Table 1). In 2000, the GISCAD group reported on a randomized phase II trial for patients with metastatic CRC previously treated with 5-FU who, upon progression, received oxaliplatin with continuous-infusion 5-FU with (FOLFOX4) or without 5-FU bolus (FOLFOX2), and observed similar efficacy in the second-line setting with an ORR of 18% versus 22%, and median overall survival (OS) of 7 versus 9 months.[8] The GERCOR group subsequently tested FOLFOX4 (with 5-FU bolus) versus induction FOLFOX7 (no 5-FU bolus) followed by maintenance continuous-infusion 5-FU and subsequent reintroduction of FOLFOX7 in OPTIMOX1, a randomized phase III study of first-line therapy in 620 patients with metastatic CRC.[9] In this trial, the ORR was 58% versus 59%, median progression-free survival (PFS) was 9 versus 8.7 months, and median OS was 19.3 versus 21.2 months, respectively. Several other investigators reported on similar efficacy results with FOLFOX regimens with and without bolus 5-FU in smaller prospective and retrospective analyses (Table 1).[10,11] FOLFIRI with and without 5-FU bolus demonstrated comparable efficacy in a few clinical trials.[12,13]

Aiming yet for higher efficacy, in the early 2000s, Italian and French investigators started testing triplet regimens with 5-FU/leucovorin, oxaliplatin, and irinotecan either without 5-FU bolus (FOLFOXIRI) in metastatic CRC[14] or with 5-FU bolus (FOLFIRINOX) in pancreatic cancer,[15] respectively. Response and survival rates were pushed even higher, albeit with increased hematologic and gastrointestinal toxicities, and randomized phase III studies subsequently confirmed superiority of the triplet over doublet chemotherapy regimens. Many contemporary studies with modified FOLFIRINOX (mFOLFIRINOX; no 5-FU bolus) noted similar outcomes with historic FOLFIRINOX, and systematic reviews and retrospective real-world data noted equally good efficacy.[16,17] As such, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) have adopted the mFOLFIRINOX regimen, in addition to standard FOLFIRINOX regimens, for both advanced CRC[18] and advanced pancreatic adenocarcinoma.[19]

No high-level evidence guidelines exist to guide practitioners on the use of 5-FU bolus in these multiagent chemotherapy regimens, although many clinicians consider the best practice is to omit the 5-FU bolus when treating elderly or frail patients, or discontinue the bolus once hematologic or acute gastrointestinal toxicities occur.

In one of the largest real-world evidence studies to date on the use of 5-FU–based regimens in advanced gastrointestinal cancers, Peng et al,[20] published elsewhere in this issue, used the Flatiron Health database to identify >11,000 patients with advanced gastrointestinal malignancies, including colorectal, gastroesophageal, and pancreatic cancers. The authors demonstrated that, after adjusting

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Table 1. Summary of Studies With Multiagent Chemotherapy With and Without 5-FU Bolus in Advanced Gastrointestinal Cancers

Study	Study Design	Cancer	Regimen	Efficacy
Mosconi et al,[8] 2000	Clinical trial	2L CRC	FOLFOX4 (+) FOLFOX2 (–)	ORR, 18.2% vs 21.8% TTP, 6 vs 5 mo OS, 7 vs 9 mo
Tournigand et al,[9] 2006	Clinical trial	1L CRC	FOLFOX4 (+) FOLFOX7 (–)	ORR, 58.5% vs 59.2% (*P*=NS) PFS, 9 vs 8.7 mo (*P*=.47) OS, 19.3 vs 21.2 mo (*P*=.49)
Aranda et al,[12] 2009	Clinical trial	1L CRC	FOLFIRI (+) FUIRI (–)	ORR, 57% vs 51% (*P*=.28) PFS, 8.3 vs 8.4 mo (*P*=.43) OS, 21.6 vs 19.2 mo (*P*=.29)
Bidard et al,[13] 2009	Clinical trial	2L CRC	FOLFIRI3 (–) FOLFIRI (+)	ORR, 17% vs 8% (*P*=.02) PFS, 3.7 vs 3.0 mo (*P*=.001)
Yoshida et al,[10] 2011	Clinical trial	1L CRC	FOLFOX6 (+) Bev FOLFOX7 (–) Bev	ORR, 53% vs 55% (*P*=NS) PFS, 12.5 vs 14.8 mo (*P*=.91)
Basilio et al,[11] 2021	Retrospective	1L CRC	FOLFOX6 (+) mFOLFOX6 (–)	PFS, 8 vs 6.6 mo (*P*=.47) OS, 29 vs 22 mo (*P*=.39)
Nakazawa et al,[17] 2023	Retrospective	1L PDA	FOLFIRINOX (+) mFOLFIRINOX (–)	ORR, 29% vs 26% (*P*=.71) PFS, 6.3 vs 5.7 mo (*P*=.44) OS, 11.6 vs 11.3 mo (*P*=.67)
Jung et al,[16] 2023	Systematic review	1L PDA	FOLFIRINOX (+) mFOLFIRINOX (–)	ORR, 28.2% vs 33.8% (*P*=.10)
Peng et al,[20] 2024	Real-world evidence	1L CRC GE PDA	FOLFOX (+/–) FOLFIRI (+/–) FOLFIRINOX (+/–)	CRC: OS, 24.4 vs 24 mo (*P*=.65) GE: OS, 10.2 vs 10.4 mo (*P*=.87) PDA: OS, 9.4 vs 9.0 mo (*P*=.58)

Abbreviations: (+), with 5-FU bolus; (–) no 5-FU bolus; 1L, first-line treatment; 2L, second-line treatment; Bev, bevacizumab; CRC, colorectal cancer; GE, gastroesophageal; m, modified; NS, not significant; ORR, overall response rate; OS, overall survival; PDA, pancreatic ductal adenocarcinoma; PFS, progression-free survival; TTP, time to progression.

for clinical factors such as performance status, comorbidities, and cancer type, omitting the 5-FU bolus in the FOLFOX, FOLFIRI, or FOLFIRINOX regimens did not jeopardize efficacy but improved safety and health resources utilization. They noted that few practitioners omit 5-FU bolus up-front from FOLFOX or FOLFIRI regimens (9% to 12% over the past decade), whereas omitting the 5-FU bolus up-front from FOLFIRINOX drastically increased from 10% to 60% over the same period. OS rates within the groups of patients with colorectal, gastroesophageal, and pancreatic cancers were no different when treated with or without 5-FU bolus up-front (Table 1). As expected, up-front 5-FU bolus conferred significantly higher rates of hematologic toxicities, including doubling the rates of neutropenia and 50% higher rates of thrombocytopenia; granulocyte colony-stimulating factor (G-CSF) utilization within 2 weeks after treatment initiation was also 50% higher.

It is unlikely that a prospective randomized phase III clinical trial of FOLFOX, FOLFIRI, or FOLFIRINOX with and without 5-FU bolus will be conducted in the United States to unequivocally address the benefit or lack thereof of using 5-FU bolus in multiagent chemotherapy regimens. Nonetheless, we now have multiple assets, including these pragmatic real-world data from Peng et al,[20] encompassing >11,000 patients treated at academic and community centers across the United States, that demonstrate no detriment in efficacy and significantly improved toxicity from omitting the 5-FU bolus up-front. Large real-world experience together with systematic reviews should exert powerful influence when they support already existing prospective clinical trials. Several reports, including Peng et al,[20] note that use of 5-FU bolus in multidrug regimens is associated with the oncologists' experience, with higher 5-FU bolus omission rates among more experienced or specialized gastrointestinal oncologists. Provider experience and access to up-to-date treatments and supportive care are likely to confer best patient-centric outcomes, leading more community oncologists to specialize in treating specific tumor subtypes, including complex gastrointestinal and pancreatic cancers. Nevertheless, it will likely take the rigorous oversight and guideline recommendations from NCCN panels, as well as the acknowledgement by the large gastrointestinal oncology community, to update our practices.

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