Letter to the editor: Re: Ratti M, Hahne JC, Toppo L, *et al.* Major innovations and clinical applications of disodium-levofolinate: a review of available preclinical and clinical data. *Ther Adv Med Oncol*. 2019

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Re: Ratti M, Hahne JC, Toppo L, *et al.* Major innovations and clinical applications of disodium-levofolinate: a review of available preclinical and clinical data. *Ther Adv Med Oncol*. 2019 Jun 4;11:1758835919853954. doi: 10.1177/1758835919853954.

I read with great interest the review article from Ratti *et al.*, from the Hospital of Cremona in Italy, reporting the clinical applications and available data related to the use of disodium-levofolinate.[1] The authors concluded that disodium-levofolinate has demonstrated a more favorable efficacy and toxicity profile in terms of overall response rate (ORR), progression-free survival, time to progression and occurrence of severe adverse events when compared with calcium–folinic acid. In addition, they noted that disodium-levofolinate allows for shortened treatment time, which has the benefit of decreasing the amount of resources required for administration and limiting the occurrence of catheter damage.

There has been very little change in the administration of high-dose fluorouracil (5-FU) with leucovorin in colorectal carcinoma in the United States since the publication of our phase II study in 1991 suggested that short-term infusional therapy of 5-FU and leucovorin was associated with an acceptable toxicity and survivability.[2] The common practice is to administer calcium salt-based levoleucovorin upfront, followed by 5-FU, due to incompatibility of the two products. The availability of sodium-based levoleucovorin, Khapzory™, as a potential alternative to the use of a calcium-based levoleucovorin, when used in conjunction with 5-FU certainly provides a new alternative for treatment of advanced colorectal cancer. Khapzory™ received US Food and Drug Administration approval under the 505(b)(2) regulatory pathway for therapeutic equivalents, meaning that it is therapeutically identical to other levoleucovorin products but is pharmaceutically differentiated as being the only sodium salt-based levoleucovorin (disodium levoleucovorin) approved in the United States.

Sodium-based levoleucovorin is compatible with 5-FU, such that both products may be combined together within the same infusion bag without the risk of calcium carbonate precipitation and potential intravenous catheter occlusion, which is included on the labels of calcium-based leucovorin products.[3] Furthermore, *in vitro* and *in vivo* experiments conducted by Di Paolo *et al.* confirmed the enhanced antitumor activity and good toxicity profile of the simultaneous combination of sodium-based levoleucovorin and 5-FU, while the sequential combination with calcium-based leucovorin failed to potentiate 5-FU activity.[4]

As highlighted in the review by Ratti *et al.*, comparative results from Bleiberg *et al.* demonstrated an observed ORR of 55% for patients treated with calcium-based leucovorin, compared with 61% for sodium-based; median overall survival durations were 11.9 months and 22.9 months ($p=0.02$), respectively and progression-free survival was 8.0 and 11.5 months. In addition, grade 3 events were 64% and 46% ($p=0.28$).[5]

Catheter occlusion may require surgical catheter removal, catheter replacement, admission or readmission to the hospital, and an increased risk of bacterial infection.[6] Although there have not been head-to-head trials comparing the efficacy of sodium-based leucovorin over calcium-based agents, as the number of patients required to support statistical superiority would have to be too large to be feasible, the primary advantages of the sodium-based formulation, in combination with 5-FU, may be a more favorable operational and safety profile, in addition to improved convenience and a time and cost-saving method of administration.[7] The increased volume of the combination of sodium-based levoleucovorin and 5-FU in the same infusion bag is negligible and non-prohibitive for patients.

As oncologists in the United States we acknowledge that the decision to make products available for use in our practices often lies with the facility pharmacy and is based on pivotal, head-to-head trials of efficacy and safety. As noted, these large trials are not available in this patient population, but the comprehensive review by Ratti *et al.*, and smaller published studies, provide compelling evidence that sodium-based levoleucovorin is therapeutically equivalent, can be administered safely as a single infusion with 5-FU with no crystallization, and has a more favorable efficacy and toxicity profile than calcium-based leucovorin, providing an important treatment option for patients with colorectal cancer.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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