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Chemotherapy options in elderly and frail patients with metastatic colorectal cancer

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Title: Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial

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Summary

Despite the fact that the majority of the patients with colorectal cancer (CRC) are ≥65 years of age, they are under-represented in clinical trials [1]. Elderly patients may be more prone than younger patients to experience chemotherapy-related toxicities secondary to existing comorbidities, incompatibility of chemotherapy with other medications, and age-related reduction in the detoxification and elimination potential of the liver and kidneys. In addition, the elderly represent a heterogeneous population [1].

Seymour et al recently published the results of FOCUS2 study that investigated below-standard-dose chemotherapy options, a comprehensive geriatric health assessment to identify factors that might aid future selection of patients or regimens and a composite measure of overall treatment utility (OTU) as objective predictors of outcome in elderly and frail patients with metastatic CRC (mCRC) [2]. After comprehensive evaluation, patients were randomized to: 48-h intravenous fluorouracil with leucovorin (group A); oxaliplatin and fluorouracil (group B); capecitabine (group C); or oxaliplatin and capecitabine (group D) at 80% of standard doses, with discretionary escalation to full dose after 6 weeks. The two primary endpoints included: addition of oxaliplatin ([A vs. B] + [C vs. D]), assessed with progression-free survival (PFS); and substitution of fluorouracil with capecitabine ([A vs. C] + [B vs. D]), assessed by change from baseline to 12 weeks in global quality of life (QoL).

The study showed that the addition of oxaliplatin vs. no addition did not result in significant PFS (median 5.8 months vs. 4.5 months; hazard ratio 0.84, 95%CI 0.69-1.01, p=0.07) and substitution of fluorouracil with capecitabine did not improve global QoL (56% in each group). Addition of oxaliplatin did not significantly increase grade ≥3 toxicities (38% vs. 32%; p=0.17), but was higher with capecitabine than with fluorouracil (40% vs. 30%; p=0.03). In multivariable analysis, fewer baseline symptoms (odds ratio 1.32, 95%CI 1.14-1.52), less widespread disease (1.51, 1.05-2.19), and use of oxaliplatin (0.57, 0.39-0.82) were predictive of better OTU.

Opinion

This study indicates that appropriate design such as below-standard doses of chemotherapy can enable to perform a randomized study in elderly and frail patients with mCRC. In addition, a comprehensive geriatric assessment can help to identify patients most likely to benefit from standard treatment. In the face of these data, providing effective care for elderly patients with CRC is an important issue, but current treatment delivery is often suboptimal. The elderly are often excluded from clinical trials by design [3] and consequently only limited data on the risks and benefits of specific regimens in this subgroup may be available.

The ageing process is associated with a gradual and continual loss of physiologic function, characterized by a reduction in organ function, including glomerular filtration, cardiac output, and hepatic volume including changes to the pharmacokinetics of a drug in the body, subsequently reducing the elimination of drugs and potentially enhancing toxicity [4,5]. In addition, hematologic function and immunologic response decline with age, and there is an increase in comorbidities and associated polypharmacy, all of which render the individual more susceptible to infection, cancer, and the stresses of chemotherapy [6,7]. As such, the risk of adverse events (AEs) associated with chemotherapy may increase while the capacity to tolerate them decreases. In addition, elderly patients may express reluctance to initiate chemotherapies that

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may adversely impact on QoL, instead placing more value on feeling well for as much of their remaining time as possible in preference to extending their lifespan. Ageing also impacts upon individuals' social network and the way they interact with society. Many elderly patients who live alone may lack the social network required to support them through temporary illness or disability related to their chemotherapy, and it has been shown that elderly individuals with few social resources to call upon and a poor economic situation are less likely to receive treatment [8].

Second important information derived from FOCUS2 study is that sequential administration of the cytotoxic agents in the treatment of mCRC has similar efficacy, and less toxicity, than front-loaded combination therapy using the same drugs, as previously shown in intriguing studies, CAIRO, MRC FOCUS and FCCD [9-11].

It is clear then that while the benefits conferred by treatment of CRC can be as significant in elderly patients as they are in younger patients, the association of chemotherapy with AEs makes treatment less appealing to older patients. The key to successful management of CRC in the elderly is individualization of treatment, taking into account not just the physiologic status of patients but also their sociologic environment and personal priorities.

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