PERSPECTIVE

Royal Australasian College of Surgeons

Current colorectal cancer chemotherapy dosing limitations and novel assessments to personalize treatments

Management of colorectal cancer is becoming increasingly more complex, with current major treatment modalities now including surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy. In the era of personalized oncology, a revised and more accurate method of determining individual chemotherapy dosing is urgently needed. Standard chemotherapy dosing is traditionally based on patient body surface area (BSA).[1] As most chemotherapy agents have narrow therapeutic indexes, and BSA is a poor indicator of optimal dose, this approach may result in supra- or sub-therapeutic drug concentrations. Consequently, many patients experience increased adverse events and dose-limiting toxicity (DLT), potentially necessitating dose reductions and/or discontinuation of treatment, or conversely, reduced efficacy and compromising clinical outcomes.

The major limitation of BSA-based dosing is it fails to accommodate variation in patient body composition parameters, including muscle mass, lean body mass and distribution. Patients with similar BSAs can have vastly different body compositions,[2] and there is growing evidence that body composition is superior to BSA in determining optimal chemotherapy dosing.[3] Some studies have reported that patients with reduced muscle density (sarcopenia) and who are obese are at the highest risk of developing DLT.[4] Overall, there is growing evidence that chemotherapy treatment dosing based on body composition, rather than BSA, reflects more accurately on drug distribution in different body compartments and thus may reduce toxicity.[5]

Clinicians routinely use several other factors to determine the initial chemotherapy dose. *A priori* dose-capping is commonly used, at varying BSA cut-offs (commonly >2m^2), despite clinical evidence showing it may not improve tolerance and may compromise outcomes.[6,7] Additionally, patient factors such as advanced age or performance status, or significant organ impairment, are used to guide dose reductions, primarily informed by clinical judgement. Individual patient tolerance will also vary due to pharmacogenomics, most notably dihydropyrimidine dehydrogenase (for fluoropyrimidines)[8] and uridine diphosphate glucuronosyltransferase 1A1 (for irinotecan).[9] Genetic variants that predict reduced drug clearance and increased toxicity are known and can be tested for. Still, limited access to testing, limited prospective data supporting routine testing and cost are all barriers that prevent uptake in routine care.

One adjunct to further improve precision medicine and reduce inter-individual pharmacokinetic variability is the implementation of therapeutic drug monitoring (TDM), a concept well-established in other specialties. Despite extensive research highlighting the advantages of TDM for 5-fluorouracil (improved efficacy and safety), BSA remains the mainstay of dosing,[10] with limited access, inconvenience and cost of testing restricting uptake.

Current research approaches to improve the assessment of body composition involve computed X-ray tomography (CT), magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry (DXA).[11,12] While CT images are routinely available, such evaluation necessitates the current gold-standard practice is time-consuming (30 minutes) as it relies on manual landmarking (selecting the correct CT slice) and segmentation (identifying body composition components). New developments in artificial intelligence (AI) provide an opportunity to automate this labour-intensive task, making it feasible as part of routine care. In addition, AI offers the opportunity to expand such measurements from a single slice to a three-dimensional composition, effectively offering a 'top to toe' whole body composition assessment.[13]

In conclusion, while many challenges remain in selecting the optimal dose for every patient, several adjuncts could be adopted to optimize chemotherapy dosing for patients with colorectal cancer. Specifically, to address the limitations of BSA-based dosing, the most promising development is embracing AI technology and implementing this software in routine clinical practice.

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