Use of the Child-Pugh score in anticancer drug dosing decision making: proceed with caution

Stefanie Krens and colleagues[1] provide a thoughtful and detailed Review on the effect of hepatic impairment in the dosing of systemic anticancer therapies. Interestingly, they suggest using the Child-Pugh score for decision making with regard to dosing for 43 (26%) of the 169 anticancer agents listed in their supplementary appendix.[1] However, we suggest that, in oncological practice, the use of Child-Pugh score for dosing poorly addresses the most common scenario of a patient with abnormal liver function secondary to hepatic metastases. We advise caution in using the Child-Pugh score for dosing recommendations for several reasons.

First, as Krens and colleagues[1] state, the Child-Pugh score was developed to predict mortality in patients with liver cirrhosis,[2] and was not developed for nor validated in patients with cancer or for dosing of anticancer agents. The authors highlight that the US Food and Drug Administration and European Medicines Agency note the importance of verifying that alterations in Child-Pugh score components are the result of liver disease,[1] and are not caused by another underlying disease, such as cancer. However, many anticancer agents are used to treat metastatic disease, a process that can impact components of the Child-Pugh score; for example, low albumin because of poor nutritional intake, or ascites related to peritoneal metastatic disease. However, Krens and colleagues[1] do not address these issues in their dose recommendations, nor are caveats added to these points. The effect of different causes of liver disease on the pharmacokinetics of gefitinib reinforce these issues.[3]

Second, aside from studies of hepatocellular carcinoma, in which affected patients often have chronic liver disease, the Child-Pugh score is not used to define patient entry into studies of anticancer agents. Rather, in most studies, concentrations of bilirubin and transaminases relative to the upper limit of normal are used to define patient eligibility, whereas diseases such as hepatitis B and C that lead to chronic liver disease, for which the Child-Pugh score would be of potential value, are often explicitly criteria for exclusion.

Third, where data are presented and used to justify the use of the Child-Pugh score, these are from small pharmacokinetic studies that do not always involve patients with cancer and, if they do, do not make it clear how they ensure that liver disease relevant to the Child-Pugh score is the predominant pathology.

The recommendation by Krens and colleagues[1] to use the Child-Pugh score to dose olaparib crystallises these issues. Olaparib is licenced as monotherapy for maintenance treatment of platinum-sensitive relapsed *BRCA*-mutated high-grade serous epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer. In two pivotal ovarian cancer studies of olaparib,[4,5] a total of 560 patients were recruited on the basis of baseline bilirubin and transaminase concentrations, and patients with hepatitis B and C were specifically excluded. Child-Pugh score data related to olaparib appears to be based on a study of 53 patients with advanced solid tumours (NCT01894243), in whom the cause of their liver disease was not described.[6,7]

If pivotal registration studies do not use the Child-Pugh score as a study entry criterion, if disease processes are in play that can influence the Child-Pugh score, and if patients with disease processes for which the Child-Pugh score is relevant are not eligible for inclusion in studies, then the scientific validity and appropriateness of using this score for dosing recommendations of anticancer drugs has to be called into question and caution advised.

We declare no competing interests.

Carlo Palmieri, Iain Macpherson
c.palmieri@liverpool.ac.uk

Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, Liverpool, L69 3GE, UK (CP); and Institute of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, Bearsden, UK (IM)

1 Krens SD, Lassche G, Jansman FGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; **20:** e200–07.
2 Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, ed. The liver and portal hypertension. Philadelphia: Saunders, 1964.
3 Horak J, White J, Harris AL, et al. The effect of different etiologies of hepatic impairment on the pharmacokinetics of gefitinib. *Cancer Chemother Pharmacol* 2011; **68:** 1485–95.
4 Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012; **366:** 1382–92.
5 Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; **18:** 1274–84.
6 Rolfo C, de Vos-Geelen J, Isambert N, et al. Pharmacokinetics and safety of olaparib in patients with advanced solid tumours and hepatic or renal impairment. 18th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; Washington, DC; March 13–18, 2017. abst PII–121.
7 Pilla Reddy V, Bui K, Scarfe G, Zhou D, Learoyd M. Physiologically based pharmacokinetic modeling for olaparib dosing recommendations: bridging formulations, drug interactions, and patient populations. *Clin Pharmacol Ther* 2019; **105:** 229–41.