

## [<sup>11</sup>C]Docetaxel and Positron Emission Tomography for Noninvasive Measurements of Docetaxel Kinetics

**To the Editor:** We read with great interest the article by Bradshaw-Pierce and colleagues (1) reporting a physiologically based pharmacokinetic (PBPK) model for docetaxel. Because docetaxel is frequently used for the treatment of several cancers, more often, recently, in combination with other anticancer agents, a comprehensive technique to evaluate the effects of other agents on docetaxel pharmacokinetics and pharmacodynamics is required. In view of this development, the PBPK model for docetaxel by Bradshaw-Pierce and colleagues is of great value. This model was developed based on measurements of docetaxel concentrations in plasma and some tissues of mice by using liquid chromatography–tandem mass spectrometry.

We would like to point out, however, that the method used might not be ideal for collecting the data to develop a PBPK model. Although liquid chromatography–tandem mass spectrometry is a sensitive technique for measuring docetaxel levels in plasma and tissue, for the latter measurements it can only be applied to animals because an extensive number of biopsies in humans is too invasive. Second, to develop a PBPK model, organ volumes and organ blood flow need to be fixed to predefined values. Furthermore, only a limited number of organs can be investigated and the validity of the model depends on an appropriate selection of these organs (before experimentation). For example, in the study by Bradshaw-Pierce and co-workers, the spleen was not selected. Uptake of docetaxel in spleen, however, is high, therefore, the spleen should be taken into account in developing the PBPK model. Finally, with liquid chromatography–tandem mass spectrometry, it might be difficult to achieve high extraction efficiency for tissue (extraction efficiency from tissues was only 40-90%), resulting in potential inaccuracies in the PBPK model (e.g., systematic errors up to 200% between simulation and measured data in the study by Bradshaw-Pierce and colleagues).

Another technique to measure drug concentrations in tissue is positron emission tomography (PET). Using this noninvasive technique, it is possible to quantify pharmacokinetics and pharmacodynamics *in vivo* in animals and humans (2). Over the years, several therapeutic drugs have been labeled with short-lived positron-emitting radionuclides. Note that with this imaging modality, only tracer doses of the radiolabeled drug

need to be administered, making it possible to predict and evaluate a dose in the same animal or human. PET measurements do not require assumptions about organ volumes and organ blood flow. In addition, the number of organs that can be investigated is not limited because a whole-body scan can easily be done. Furthermore, PET has high accuracy and sensitivity (picomolar level).

To investigate tracer kinetics of docetaxel, we have labeled this drug with carbon-11 at high specific activity (>18.5 GBq/μmol; ref. 3). This enables sensitive and appropriate measurements of [<sup>11</sup>C]docetaxel uptake in tissues. Using [<sup>11</sup>C]docetaxel, we have done a preliminary biodistribution study in healthy male Wistar rats at 5, 15, 30, and 60 min and found that the spleen had the highest uptake followed by urine, lung, and liver. Brain and testes showed the lowest uptake. Within less than 5 min, [<sup>11</sup>C]docetaxel had already cleared from blood and plasma by >99%. Because docetaxel binds intracellularly to tubulin, knowledge of the uptake of docetaxel in the separate organs of the intracellular component (e.g., heart, liver, spleen, lung, but also tumor tissue) is required. We agree with Bradshaw-Pierce and co-workers that this will contribute to a better understanding of the toxicity and tumor response of docetaxel. We believe, however, that PET is a more accurate and sensitive technique for measuring docetaxel kinetics. Therefore, we have embarked on [<sup>11</sup>C]docetaxel PET studies in animals and humans with advanced solid tumors with the ultimate goal of predicting response to docetaxel therapy in individual patients.

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