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ImmunoPET to Optimize the Dose of Monoclonal Antibodies for Cancer Therapy – How Much is Enough?

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Footline: ImmunoPET for Optimizing the Dose of Monoclonal Antibodies

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Monoclonal antibodies (mAbs) have emerged as one of the most effective and least toxic classes of personalized medicines for cancer (*1*). These drugs rely on specific recognition of a target receptor for their anti-tumor effects. The receptors may be expressed on tumor cells or stromal cells (e.g. vascular endothelial cells) or in the case of immunotherapy which is aimed at immune checkpoints, by tumor cells or immune effector cells (e.g. T-lymphocytes). The clinical development of mAbs follows a pathway applied to all drugs which includes Phase 1 first-in-humans trials (FIHT) to assess safety, Phase 2 trials to study their effectiveness in a selected patient population and large randomised Phase 3 trials that lead to regulatory approval and product registration (*2*). Most FIHT of mAbs have employed a clinical trial design that is commonly used for small molecule cytotoxic agents, in which escalating doses are administered to patients to identify the maximum tolerated dose (MTD). Based on the MTD, the recommended dose is selected for Phase 2 trials. However, this Phase 1 design is inherently flawed for FIHT of mAbs because it assumes that the effectiveness and normal tissue toxicity of the drug increases in direct proportion to the administered dose. Since mAbs exhibit saturable binding to their target receptors, one could envision that there is an optimal dose that results in maximum receptor occupancy and yields maximum therapeutic effect. Higher doses would not be expected to provide additional therapeutic benefit, but could increase the risk for toxicity. Moreover, in contrast to cytotoxic small molecule drugs, most mAbs have an excellent safety profile. A survey of 82 FIHT of mAbs revealed that in 47 of these studies (57%), dose-limiting toxicity (DLT) was not found and the MTD was reached in only 13 trials (16%) (*3*). Instead, the planned maximum administered dose (MAD) was achieved in all trials, attesting to the excellent safety profile of these drugs. Since the MTD was not identified, in most cases, the Phase 2 trial dose was selected based on the MAD or in some cases on the pharmacokinetic properties of the mAbs in order to achieve a blood concentration in humans shown to be effective in preclinical studies. In one review of 27 mAbs studied in a total of 60 Phase 3 registration trials, the dose examined and eventually approved by the U.S. Food and Drug Administration was actually lower than for Phase 2 testing (*4*). Although these doses of mAbs proved effective, there remains considerable uncertainty about whether or not they are optimal for cancer treatment. Clinical trial designs that attempt to define a “biologically effective dose” (BED), i.e. a dose that is mechanistically optimal have been proposed as a more rational approach for dosing mAbs for cancer treatment (*5*). However, identifying the BED requires a biomarker that reports on interactions of mAbs with their target receptors to assess if the dose is sufficient to yield the desired biological effects. Ideally, such a biomarker should be readily accessible and not require a tissue biopsy due to the impracticality of sampling all lesions either spatially or temporally in patients. ImmunoPET is a powerful non-invasive tool to assess the tumor uptake of mAbs at any location in the body. Furthermore, immunoPET offers the opportunity to interrogate receptor occupancy in patients treated with mAbs, since positron-emission tomography (PET) is quantitative, which could potentially provide a biomarker to select the BED (*6*). ImmunoPET employs mAbs labeled with positron-emitting radionuclides, most commonly ^{89}Zr [$E\beta_{mean}$ = 0.40 MeV (23%); $t_{1/2phys}$ = 78.4 h). Interestingly, preclinical studies of immunoPET routinely report the effect of administration of an excess of unlabeled mAbs on the tumor uptake of the radiolabeled mAbs, to confirm the the specificity of tumor localization (*7*). These “blocking” studies actually reveal receptor occupancy by the unlabeled mAbs, which results in decreased tumor uptake of the radiolabeled mAbs. These studies do not identify the optimal dose of the unlabeled mAbs required to block uptake of the radiolabeled mAbs though, because they examine only administration of a large excess of the unlabeled mAbs for blocking. To identify the optimal dose would require titration of the effect of increasing doses of unlabeled mAbs on the tumor uptake assessed by immunoPET.

In this issue of the Journal, Menke-van der Houven van Oordt et al. report an immunoPET study with ^{89}Zr-labeled GSK2849330 anti-human epidermal growth factor receptor-3 (HER3) mAbs in 6 patients with HER3-positive tumors (*8*). Tumor and normal tissue uptake were evaluated and the effect of therapeutic doses of GSK2849330 mAbs (GlaxoSmithKline) on tumor uptake was assessed as an indicator of receptor occupancy. This report follows an earlier pre-clinical PET study in which ^{89}Zr-GSK2849330 mAbs (0.5 mg/kg; 5 MBq) were administered to mice with HER3-positive CHL-1 human melanoma xenografts or HER3-negative MIA-PaCa-2 human pancreatic tumors (*9*). In this earlier study, PET showed lower uptake of ^{89}Zr-GSK2849330 in MIA-PaCa-2 compared to CHL-1 tumors, and tumor uptake of ^{89}Zr-GSK2849330 was blocked by pre-administering a 100-fold excess of unlabeled GSK2849330 (50 mg/kg), revealing that tumor uptake was HER3 specific. An interesting finding in this preclinical study was that co-administration of increasing mass doses of unlabeled GSK2849330 (0.3-10 mg/kg) with ^{89}Zr-GSK2849330 (0.14 mg/kg) increased tumor uptake rather than decreased uptake, due to lower liver accumulation and a prolonged residence time of ^{89}Zr-GSK2849330 in the blood. This is an example of target mediated drug disposition (TMDD) characteristic of mAbs mediated by interaction of the Fc-domain of the mAbs with Fcγ-receptors on hepatocytes, causing non-linear pharmacokinetics which prolong circulation times at higher mass doses (10). TMDD is also be caused by interaction of mAbs with their target receptors on tumors and other tissues (11).

In the current clinical study (*8*), it was determined that an 8 mg mass dose (37 MBq) was sufficient to avoid rapid elimination of ^{89}Zr-GSK2849330 from the blood. This dose provided liver uptake equivalent to a larger mass dose (24 mg), and permitted tumor visualization (8). PET scans were acquired at 48 h and 120 h post-injection (p.i.) of ^{89}Zr-GSK2849330. Patients received a baseline PET scan with ^{89}Zr-GSK2849330, then 14 days later were treated with

GSK2849330 (0.5, 1.0 or 30 mg/kg) and PET images were again acquired at 48 h and 120 h p.i. of ^{89}Zr-GSK2849330. The tumor uptake of ^{89}Zr-GSK2849330 at 120 h p.i. was quantified on the baseline PET images by a peak standard uptake value (SUV_{peak}) and compared with post-treatment scans. In addition, the tumor uptake of ^{89}Zr-GSK2849330 was modeled by a compartmental pharmacokinetic model that incorporated tissue and plasma concentrations of radioactivity and modeled the HER3-mediated binding and internalization of GSK2849330 by tumor cells. Based on this modeling, a Patlak plot was applied to identify the inhibitory dose-50% (ID_{50}) and ID_{90} of GSK2849330 for interaction with HER3 receptors (12). There was large variability in uptake of ^{89}Zr-GSK2849330 between cancerous lesions in an individual patient and between tumors in different patients, with SUV_{peak} values ranging from 1.26 to 15.26. Heterogeneous tumor uptake of ^{89}Zr-trastuzumab has been reported on PET images of patients with HER2-positive breast cancer (13). There was also considerable variability in the changes in tumor uptake of ^{89}Zr-GSK2849330 observed following administration of therapeutic doses of GSK2849330. Nonetheless, an important finding was illustrated in one patient with ovarian cancer, in which tumor uptake of ^{89}Zr-GSK2849330 decreased by more than 2-fold after administration of a therapeutic dose of GSK2849330 (30 mg/kg). By Patlak analysis, the investigators were able to estimate the ID_{50} and ID_{90} for binding of GSK2849330 to HER3 receptors, which were 2 mg/kg and 18 mg/kg, respectively. These BED are lower than the MTD for GSK2849330, which was 30 mg/kg. This suggests that immunoPET could be valuable to assess receptor occupancy by mAbs, and if appropriately incorporated into a clinical trial design could aid in selecting the optimal dose of mAbs for cancer treatment, i.e. the BED. To fully validate this approach would require imaging studies in groups of patients administered increasing mass doses of the therapeutic mAbs with immunoPET performed prior to and after treatment to ascertain the level of receptor occupancy. Furthermore, successful application of immunoPET as a biomarker to identify the BED, would require confirmation that the level of receptor occupancy determined by immunoPET predicts therapeutic outcome in patients treated with the mAbs.

The application of immunoPET to probe receptor occupancy in tumors was reported for another HER3 mAb, lumretuzumab (University Medical Center, Groningen, Netherlands) labeled with ^{89}Zr (14). Patients with HER3-positive tumors received a baseline immunoPET study with ^{89}Zr-lumretuzumab, then were treated 14 days later with 400, 800 or 1,600 mg of lumretuzumab. PET was repeated to examine changes in tumor uptake of ^{89}Zr-lumretuzumab. Important to note is that it was necessary to combine 100 mg of unlabeled lumretuzumab with ^{89}Zr-lumretuzumab (1 mg) for PET to avoid rapid elimination from the blood and high normal tissue sequestration in order to obtain good quality images. This is another example of TMDD of mAbs. Administration of therapeutic doses of lumretuzumab (400-1,600 mg) caused a 12-25% decrease in tumor uptake of ^{89}Zr-lumretuzumab. However, the mass dose of lumretuzumab required to obtain maximum receptor occupancy was not found, since no plateau was reached over the dose range studied. Nonetheless, this report and the study described by Menke-van der Houven van Oordt et al. both suggest that immunoPET is a promising tool to assess receptor occupancy in tumors which may aid in optimizing the dose of mAbs required for cancer treatment.

HER3 is a member of the human epidermal growth factor receptor (EGFR) family that is expressed in ovarian, breast, prostate, gastric, bladder, lung, melanoma, colorectal and squamous cell carcinoma (15). HER3 overexpression has been implicated in resistance to cancer treatment. There have been only a few reports of immunoPET to assess expression of HER3 on tumors preclinically (9, 16) or clinically (14, 17). The immunoPET studies reported by Menke-van der Houven van Oordt et al. (8) and by others (14, 17) demonstrate the feasibility of imaging HER3 in patients with cancer, which may yield information on resistance pathways or aid in selecting patients for treatment with HER3-targeted mAbs. The potential for immunoPET to optimize the dose of HER3 mAbs by assessing receptor occupancy could be a powerful tool.

DISCLOSURE

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