Personalized Medicine: Through the Looking Glass of Functional Imaging

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Abstract

Imaging techniques afford opportunity to personalize chemotherapy delivery by prospectively determining how much of an agent is delivered to which tumor site. Drug distribution can be prescribed by altering the properties of the drug (nontechnology) or the physiology of the host (induction of alterations of blood flow).

Manuscript

In this issue of *Clinical Cancer Research*, van der Veldt and colleagues (1), provide a glimpse into the future. They provide real-time *in vivo* distribution of docetaxel at normal therapeutic doses and infusion rates to tumors, and potentially normal tissues, in *H. sapiens* (HUMANS!).

For some time positron emission tomography (PET) scans and short lived positron emitters have revolutionized how various diseases are assessed at initial diagnosis and in response to therapies (2-7). PET has impacted drug discovery with earlier *in vivo* proof of target validation. (8-12) For cancers and other diseases, hitting the target is associated with better efficacy, while missing the target results in greater toxicity. The contribution of this study by van der Veldt, et. al. is that its findings afford opportunity to more specifically address these concepts at the tumor, and perhaps cellular, level and to allow for more precise drug development and therapeutic targeting.

A fundamental question is to prospectively determine the anticipated concentration of a chemotherapeutic agent in tumors in an individual patient. For example, how much drug actually gets to a tumor? If a patient has a 20 x 20 x 20 cm or 8000 cm$^3$ of tumor there may be as much as $10^9$/cells/cm$^3$ of tumor or 8 x $10^{12}$ tumor cells. If one takes a typical dose of 75 mg/m$^2$ or 150 mg of docetaxel and applies Avogadro’s number, then one can estimate that $1.05 \times 10^{20}$ molecules of docetaxel were administered.* If the molecules only distributed to the tumor mass, then there would be $1.31 \times 10^7$ molecules per cell and an improbable intracellular concentration of 21.8 µMolar (174 µM/8L). If one assumes the docetaxel were distributed homogeneously in this hypothetical 200 pound person (91 kg) there would have be an average concentration of 1.91 µMolar (174 µM/91L) in the tumor and in the normal tissue as well. As is clearly evident, these calculations fail to take into account almost everything we know about drugs such as intravenous infusion time, area under the curve, systemic clearance rate, blood flow to the tumor compartment of interest, tumor clearance of the agent, volumes of compartments and distribution, and polymorphisms of drug clearance, to name but a few.

The technique detailed by van der Veldt, et. al. allows for experimental determination of docetaxel concentrations. The subjects largely had non-small cell lung cancers and were initially dosed with tracer amounts of $[^{11}C]$docetaxel. The PET intensity in a central vascular compartment (aorta) was determined. This was done hours later when $[^{11}C]$docetaxel was readministered, now with a standard dose of $[^{12}C]$docetaxel. The now diluted, but known, specific activity of the radiolabel and correlation of PET intensity of the central compartment to measured docetaxel blood levels afforded the ability to calculate the accumulated amount of docetaxel in tumors during the scan that followed therapeutic dosing of docetaxel. Remarkably, this uptake in the lung tumors was fairly tightly distributed and ranged from 0.669 to 1.921 µg/cm$^3$. (Table 1 in the supplemental data.) This would be a range of 0.776-2.23 µMolar. This result is comparable to the calculated value above suggesting that there is not enhanced distribution of docetaxel to the tumor.
An additional point of interest in this current study is that in the two subjects for whom doxetaxel in both the primary cancer and lymphatic metastases could be assessed (Table 1 in the supplemental data, patients 3 and 4), the accumulated levels of docetaxel were lower in the primary tumors as compared to the lymphatic metastatic sites.

With the small numbers of patients included in this study there was not a significant correlation of tumor response by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, and tumor uptake of doxetaxel. Nevertheless, the patient with the best response (supplemental data patient 5) had the highest tumor uptake of docetaxel. In this age of Bayesian and adaptive clinical trial designs, it is clear that the future might involve directing therapy to those patients for whom tumor uptake of trace chemotherapeutic is highest to maximize response and systemic exposure the lowest to minimize toxicity. Shown in figure 1 panel A are scans from a patient with a left upper lobe lung cancer. In panel B the redder colors are associated with more metabolic activity and in panel C for the drug the white and yellow indicate high levels whereas the green and blue very low levels. In this patient the optimal distribution of the drug activity would ideally match the metabolically active tumor and spare normal tissues. Although today the cost of such a trial run with isotopic tracers is prohibitive, tomorrow might bring new techniques and intentions that make the cost of the companion pretreatment “trial run” economically sound. We would not dose all patients with a particular disease with increasingly expensive therapeutics, rather only those for whom the drug can be targeted to the tumor. It would also be intriguing if the scans described in this manuscript, could be simultaneously done with traditional [15F]deoxyglucose scans. In this manner it might be that tumors that are most metabolically active and have the greatest traditional SUV readings also have the greatest number of pharmacophores for the doxetaxel to target, such as the microtubular structures that might be associated with intense mitotic activity.

It is clear that expansion of this technique affords opportunities to revealing intricacies of drug distributions to different cancers and cancers in different sites. Examples include measuring the pharmacological results of intraarterial infusions directly into tumors. Nanotechnology techniques to selectively target small molecules to tumors by taking advantage of delivery particle size and vascular characteristics can be critically assessed. Finally, one might envision pharmacological direction by selectively altering tumor as compared to normal tissue blood flow. PET imaging of micro-dosed chemotherapeutic agents as described in this paper opens the door for validating these and many other possibilities. Thus the future is bright. On the molecular side we have the improved knowledge of tumor cell heterogeneities, on the pharmacological side improved understanding of how drugs might be selectively distributed to tumors, and on the in vivo systems biology side an ability to measure the aggregate of all of the above. This strategy is contrary to the reductionist approach of the past. This manuscript provides us a look to the future. Just like Alice peering through the looking glass, what we see is only becoming better defined and may be tomorrow’s reality.

Footnote
* calculations: docetaxel molecular weight = 861.9 gms/mole; moles docetaxel administered with a 150 mg dose = (0.15 gms)/(861.9 gms/mole) = 1.74 x 10^{-3} moles or 174 µmoles; # docetaxel molecules administered with a 150 mg dose = (0.15 gms)(6.022 x 10^{23} molecules/mole)/(861.9 gms/mole) = 1.05 x 10^{20}; concentration of doxetaxel in the tumor ranged from 0.699-1.921 µg/cm^3; (0.669 µg/cm^3)(1000 cm^3/liter)/(861.9 µgm/µmole) = 0.776 µMolar; (1.921 µg/cm^3) (1000 cm^3/liter)/(861.9 µgm/µmole) = 2.23 µMolar

The author has no conflicts of interest pertaining to this paper.
References:


Figure 1 Shown in panel A are 3 traditional computerized tomography (CAT) scans in a patient with a left upper lobe lung cancer. Panel B shows the same images from a [15F]deoxyglucose PET scan. Panel C is a hypothetical PET scan of a microdose of a therapeutic agent.

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The scans in Figure 1 were kindly provided by Michael M. Graham, M.D., Ph.D., Professor of Radiology, and Director of Nuclear Medicine at the University of Iowa, Iowa City, IA 52242.
Figure 1:
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