PET Imaging of Tumor Growth: Not as Easy as It Looks

Anthony F. Shields

Positron emission tomography can be used to image tumor proliferation when combined with appropriate labeled tracers, such as the thymidine analog $^{18}$F-3'-deoxy-3'-fluorothymidine. Although thymidine kinase 1 is the principal mechanism of cell trapping, other variables, such as the cellular level of native thymidine, may need to be considered. Clin Cancer Res; 18(5); 1189–91. ©2012 AACR.

In this issue of Clinical Cancer Research, Zhang and colleagues (1) discuss the use of $^{18}$F-3'-deoxy-3'-fluorothymidine (FLT) and positron emission tomography (PET) in xenografts to measure tumor growth. In their study, variations in the level of native thymidine affected the avidity of the tumor for the tracer.

PET, which is now routinely used in clinical oncology, generally employs fluorodeoxyglucose (FDG) to detect tumors and assess their metabolic activity. Because FDG measures only one aspect of the energetic pathway, investigators have developed other tracers to assess different aspects of metabolism in tumors and normal tissues. FLT, a thymidine analog, was developed to measure cell proliferation because it is trapped in the DNA synthetic pathway (2). Previous PET methods used thymidine itself, labeled with $^{11}$C, but the 20-minute half-life of this tracer precludes its use in preclinical models.

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in mice and rats than in dogs and humans (7). In some preclinical studies, the high level of thymidine in rodents was shown to decrease tracer uptake. The reliance by Zhang and colleagues on murine xenografts in their study may alter our ability to fully translate their results to patients.

From the bloodstream, FLT and thymidine are transported across the cell membrane by both equilibrative (ENT1 and ENT2) and concentrative (CNT1 and CNT3) transporters, which have different affinities for thymidine and FLT (8). The added complexity of the conformation of the transporters and how these differences may affect FLT retention require further study. Once in the cell, the exogenous thymidine and FLT obtained from the blood mix with the endogenously synthesized pool of thymidine. In the implanted cell lines studied by Zhang and colleagues, this pool was shown to vary significantly and compete for the trapping of FLT. It remains to be determined how common a problem this is in tumors clinically. Most of the thymidine that is used by cells in DNA synthesis comes from endogenous synthesis. Once in the cell, FLT can be metabolically trapped by phosphorylation by TK1. As noted above, TK1 and cell proliferation generally increase concomitantly; however, the control of TK1 is complex and includes posttranslational mechanisms. Drugs that interfere with the endogenous synthesis of thymidine can produce rapid increases in TK1 activity and lead to marked retention of labeled thymidine and FLT (9).

This “flare” phenomenon can be used in pharmacodynamic measurements of the effect of agents that block thymidylate synthase (TS), such as 5-fluorouracil and nalatrexol.

We also need to consider the normal distribution of FLT in various organs in vivo. Little FLT is seen in the brain because of the low proliferative rate and the inability of thymidine and FLT to cross the intact blood-brain barrier. When the blood-brain barrier is broken down in tumors, high contrast is seen compared with normal brain parenchyma (10). FLT retention may be seen in the brain when breakdown occurs because of tissue necrosis or when inflammation is present. Inflammatory cells anywhere in the body, which often are proliferating, can retain FLT and incorrectly suggest that a tumor has spread. Some investigators have shown that FLT can be used to image the effects of immunotherapy (11).

This brief summary highlights some of the variables that can alter the tumor retention of FLT. Fortunately, many of these variables become less important when one compares a baseline and post-treatment scan in a single patient. Zhang and colleagues (1) found that FLT retention readily measured the effect of treatment when used in tumors that showed increased FLT uptake at baseline. FLT appears to be a promising method for assessing response to treatment; however, investigators need to understand its mechanism of retention. Such information is important for a proper interpretation of the results obtained with any tracer in...
oncology, because PET imaging of tumor growth is not as easy as it looks.

Disclosure of Potential Conflicts of Interest

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