Motexafin Gadolinium (Xcytrin) with WBRT for Brain Metastases?

A novel agent called motexafin gadolinium (MGd), with a marketed name of Xcytrin, has been studied as a potential neuroprotectant as well as radiosensitizer that may allow patients with brain metastases to do better when it is added to whole brain radiation therapy (WBRT) than they would with WBRT alone. It is a molecule called a metallotexaphyrin, which forms stable complexes with large metal cations and accumulates preferentially in tumor cells (reference abstract here). It is readily detectable by MRI, and in fact some have suggested that no matter what else it may do, it could be a remarkably sensitive tool for picking up brain metastases. Here is an example of how good is is at identifying metastases on a brain MRI, and how well it localizes in brain tumor tissue:

![Brain MRI](image)

It inhibits an enzyme called thioredoxin reductase, which can be overexpressed in lung cancer, in which it is associated with aggressive disease, tumor resistance, and worse survival. MGd generates reactive oxygen species by catalyzing the oxidation of several intracellular-reducing metabolites, which leads to radiosensitization (stronger effects of radiation)(abstract here).

In an early trial testing the value of WBRT with or without MGd (an IV drug given before each of 10 RT fractions over two weeks) for patients with brain metastases in 401 patients (abstract here), there was only a minimal, non-significant increase in median survival and actually an approximately one-month improvement in neurologic progression (8.3 months for WBRT alone, 9.5 months with MGd; not statistically significant). However, 251 of the patients on the trial had NSCLC, and among that subset, there was actually a statistically significant increase in time to neurologic progression, as assessed by a blinded, independent events review committee that did detailed neurologic testing (median 7.4 months for WBRT alone vs. median not reached for WBRT with MGd):

![Brain MRI](image)

It did appear that the addition of MGd led to improved memory and overall neurologic function in patients with brain metastases from NSCLC. It's not clear why this effect is specific to NSCLC over SCLC, although it may be because patients with NSCLC can have a slower pace
of disease and prolonged survival after treatment for brain mets. Regardless of the reason, the encouraging results thus far have been limited to brain metastases from NSCLC.

In order to clarify this issue, Dr. Minesh Mehta, a radiation oncologist and expert on brain metastases at the University of Wisconsin who led the earlier trial, conducted a later trial that he presented at ASCO 2006 (abstract here). This study enrolled 554 patients with brain metastases from NSCLC from all around the world to receive WBRT with or without MGd, looking for a significant improvement in time to neurologic progression. There was an overall trend of favorable results for the folks who received MGd with WBRT, but it wasn’t statistically significant:

Interestingly, though, the investigators noted that the patients from the US and Canada, who accounted for a little over half of those enrolled, were far more likely to start WBRT within just a few weeks after diagnosis than patients in Europe or Australia. The improvement in time to neurologic progression was striking and was actually statistically significant if they looked only at the patients who started WBRT within four weeks of diagnosis, or looking only at the patients diagnosed and treated in North America:

So this wasn’t an unalloyed success, but there was certainly indications of value from MGd. At this point, this agent has not been approved by the FDA, and it is not commercially available. In the meantime, it would also be a great help in identifying brain metastases. We’ll see if it becomes available as a new tool at some point.