Japanese Variant on Adjuvant Chemotherapy: The Story of UFT

Throughout multiple discussions of adjuvant chemotherapy, I’ve focused on the traditional approach used in the US and Europe of 3-4 cycles of platinum-based chemo, treating for up to about three months with a rather intensive approach. However, in Japan, they’ve studied the value of a different form of adjuvant treatment, with a drug called UFT that is generally well-tolerated, mild, and taken for 1-2 years by mouth. It’s not commercially available in the US and, unfortunately, is not even being studied outside of Japan because US investigators haven’t been able to get access to run trials with it. But it does provide some more insight about the potential value of an alternative approach that my friend and surgical colleague Eric Vallieres has referred to as MILD, for minimal, indefinite, and low dose. Trials such as the RADIANT study (post here) and vaccine-based work are variations on that theme.

UFT is a combination of two drugs, tegafur and uracil. Tegafur is an oral chemo drug in the same family as an old chemo standard called 5-FU, and the uracil it’s packaged with in UFT helps inhibit the body’s breakdown of the active form. Taken together, it may lead to prolonged exposure to this anticancer drug taken orally on a long-term, daily basis. Side effects are quite mild overall, with a minority of patients experiencing nausea/vomiting, diminished appetite, or abnormal liver tests.

Back in the original meta-analysis of post-operative chemotherapy benefits, now more than 10 years ago (paper here), UFT was classified under “other” drugs and showed a strong trend toward a survival benefit in the three included studies, but even together these trials didn’t have enough weight to be statistically significant. But around that same time (1996), a paper came out of Japan (abstract here) that randomized 323 patients with resected stage I to III NSCLC (about 2/3 with stage I disease) to either no post-operative treatment, UFT for a year, or two cycles of cisplatin-based chemo followed by a year of UFT:

![Contribution of UFT as Adjuvant Therapy for Early Stage NSCLC](image)

Wada, JCO 1996
The results showed that both of the groups that received UFT did significantly better than the group of patients that were only observed, and there was no clear advantage to the combination of cisplatin-based chemo to UFT:

![Graph showing survival rates](image)

It appeared that patients with adenocarcinomas received more benefit.

We didn’t hear much about UFT for several years, but then around 2003, Kato and colleagues out of Japan reported results at ASCO that were subsequently published in the New England Journal of Medicine (abstract here). This study enrolled an amazing 999 patients with stage I lung adenocarcinomas after resection (why couldn’t they just enroll one more for an even thousand) to receive observation or up to two years of UFT (250 mg/m2 per day) as adjuvant chemotherapy. The results were quite amazing. First, the 5-year survival was 85% even in the control group (no chemo), which is remarkable. It’s hard to know why they did so well in this Japanese series, but I suspect that a large part of it is because a huge proportion of these stage I adenocarcinomas were in the BAC range, likely with a much more favorable prognosis than other NSCLC subtypes, stage for stage. In any event, the trial showed a significantly better result in favor of recipients of UFT, although the absolute improvement in survival was only 2.5%:
Amazingly, the curves ran together for four years and didn’t begin to separate until the four year mark. This is very unlike the curves on trials of adjuvant chemo with cisplatin-based chemo, which generally included more higher stage patients. Presumably, with patients who have such a favorable prognosis (stage I, and especially if there are many BAC lesions), it takes as long as four years to see the differences of even an effective treatment.

But this trial also showed that the benefit was driven entirely by the patients with T2 cancers (3 cm or larger, or involving the pleura, the lining around the lung). The survival was completely identical for in the patients with T1 cancers, who were the majority, comprising nearly 3/4 of those on the trial, but the survival benefit was quite striking for the minority of patients with T2 adenocarcinomas:
In patients with T2 adenocarcinomas, the survival benefit was more than 10%, very highly significant, and it appears that the curves separate before the four year mark. I’m just speculating, but it could be that in Japan, focusing on T2 instead of T1 adenocarcinomas may have been significant because it removed a large proportion of very indolent BAC lesions that were much more likely to present as small ground glass opacities than larger tumors.

In the meantime, there were a few trials that didn’t clearly demonstrate a value for UFT. In the setting where there are some positive and some negative trials, a meta-analysis can be helpful, pooling together the data from a bunch of trials. This was done for UFT and published by Hamada and colleagues (abstract here). Including just over 2000 patients from 6 trials, the vast majority looking at stage I patients only, they reported a highly significant improvement in 5 and 7 year survival when 1-2 years of UFT was administered after surgery:
Although US investigators have been very interested in running trials of UFT in the US, it hasn’t been possible to get access from the Japanese company that makes it. There has never been a confirmatory study, and because we have seen a growing body of evidence that illustrates how differently treatments work in Japan and other parts of the world, nobody can draw any conclusions about whether drugs like UFT (I would consider a drug called capecitabine, or Xeloda, to be the closest thing, as an oral form of 5-FU) really would help a worldwide population.

Overall, this represents a different approach to standard chemo, which is far more intense over a shorter period of time. The trial by Kato and colleagues did report that compliance became an issue for patients, whether because of annoyance with mild ongoing side effects or just getting sick of taking medication daily. In that study, only 61% of patients were still taking it after two years.

With tarceva commercially available and several other targeted oral agents in clinical trials, it will likely become quite possible to test whether a milder, long-term strategy for adjuvant treatment improves survival, either added to or instead of more toxic standard chemotherapy. In the meantime, with the detrimental effect of maintenance gefitinib demonstrated after chemo/radiation for stage III NSCLC (post here), I’d still remain cautious about adding new treatments that may or may not pan out as beneficial until we actually get the results of trials.

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