Early Disease Control: More Predictive of Clinical Benefit than Response

In my last post, I described our evolving recognition in the lung cancer field that significant response as the threshold for clinical benefit is too high and that stable disease is likely a relative benefit as well. An important trial presented by Dr. Lara at UC Davis at ASCO (our biggest cancer meeting) in June, 2006 (abstract here) highlighted not only that disease control rate (DCR), or “non-progression” is more predictive of improved survival outcomes than response rate (RR), and that the prediction can be made reliably in the second month after starting treatment, usually after two cycles of chemo (I recently wrote about early follow-up PET scans to predict outcome in advanced NSCLC, but a CT scan after two cycles of chemo is much more commonly practiced).

Obviously, disease stage is the most important factor in predicting survival in cancer patients. Staging is designed to separate anticipated survival into various groups. But when I meet new patients just starting on therapy, I tell them that the second key piece of information that we don’t have yet is how responsive their cancer is. Dr. Lara’s study demonstrates that we can get a good idea of longer term outcomes within the first couple of months, and that the survival of patients with stable disease is closer to that of responders than that of progressors.

His presentation described data pooled from three large randomized trials conducted by the Southwest Oncology Group over the past decade, which included 984 patients in total:

![Randomized SWOG Trials in Advanced NSCLC](image)

(click to enlarge)

The actual studies don’t matter much — there were no significant differences in outcomes between the two arms in any of them, and they all had a patient population representative of the kinds of patients who are on US-based clinical trials in lung cancer: median age 62, 2/3 men, generally good performance status. Looking at all of the results together, the RR was 27%, and responses occurred within two months (essentially, at the time of first repeat CT).

Not surprisingly, the median survival was much better in patients who showed a response (15 months) than in those who showed progression (5.2 months). Patients with stable disease fell in between, but closer to responders (10.4 months). These results are illustrated in the following figure showing survival curves:
The last point is that the survival benefit of patients with a response or SD is set by month 2, and repeat assessment of response at month 3 or 4 does not add more information. Here, survival benefit is measured as a “hazard ratio” (HR) again, where a decimal less than one means an improvement in survival compared to the other group, in this case patients who show progression on their scans. So a HR of 0.42 represents a 58% improvement in survival compared with the reference group (HR set at 1.0), while a number higher than 1, like 1.38, would represent a 38% worsening of survival in that group.

So how well a person’s cancer responds after the first two cycles will often provide a good prediction of survival, with progression vs. non-progression or disease control being the biggest difference. However, most of this work was done in the years before targeted therapies like EGFR inhibitors, which probably are more of a wild card after treatment, since there are definitely patients who show early progression on chemo and then do remarkably well with igurea or tarceva. However, as far as conventional chemo goes, the first couple of cycles provides a good litmus test of how someone is likely to do with chemo-based treatment in the future.

These findings are interesting, but this is the first time we’ve seen this kind of analysis and the suggestion that DCR is more important than RR. We need to get more information to clarify whether these results are seen with other trials. However, if validated, these results also imply that we could take an early look at overall differences in DCR after just a few months of a clinical trial in order to assess which treatment is likely to be better. This would mean a potential to separate useful new treatments from less useful ones faster than we can do using our current approaches, so we might bring new approaches into clinical practice earlier.