The Genitourinary (GU) Cancer Committee of the Southwestern Oncology Group (SWOG) has achieved repeated successes in conducting prospective studies of prostate cancer. This article is a summary of recently completed and current trials in prostate cancer and, as such, represents an intriguing snapshot of priorities in prostate cancer clinical trials in 1997.

Bilateral Orchiectomy With or Without Flutamide
The most provocative recent trial, and one which can be anticipated to reverberate for decades through the prostate cancer literature, is the recently analyzed comparison of bilateral orchiectomy with or without flutamide (Eulexin) for D2 prostate cancer. This trial is of landmark importance. It represents the 27th randomized prospective trial of total androgen blockade compared to monotherapy performed since 1979. It is unique because of its large size (about 1,300 patients). Few clinical questions in all of medicine have been subjected to so many prospective clinical trials as that of combination vs monotherapy for advanced prostate cancer. Ironically, the results of these numerous trials are contradictory. In 1995, the Prostate Cancer Trialists Cooperative Group (PCTCG) subjected 22 of these trials published up to 1994 to a meta-analysis.[1] Although there was a trend toward a benefit of total androgen blockade, it was not significant at 95% confidence limits. This threw substantial doubt on the benefit of total androgen blockade.

This meta-analysis has been criticized. In particular, many of the trial studies were of relatively poor quality, and a number were unpublished. For a number of these trials, there was no data regarding such important issues as concealment of randomization, (ie, the effectiveness of blinding) patient selection, and adequacy of follow-up. A sensitivity analysis, which ranked the published studies according to their quality, demonstrated that a benefit of total androgen blockade was demonstrated if the least well done studies were excluded from the meta-analysis.[2]

Thus, controversy continues to rage over the benefit of total androgen blockade. The limitations of meta-analysis are well known. Meta-analysis is retrospective and subject to bias. Methodologists agree that there is no substitute for a large, well-done, randomized trial. Therefore, the results of the SWOG trial have been anticipated with eagerness. It was hoped that this trial would provide the final proof for the benefit (or lack thereof) of total androgen blockade.

The trial, in fact, demonstrated a lack of benefit for the addition of flutamide to bilateral orchiectomy. This raises a difficult question. The earlier SWOG trial showed a clear benefit of flutamide plus daily leuprolide (Lupron) injection compared to leuprolide alone. Both trials were large and carefully carried out. Both trials seem conclusive.

How does one explain the different outcomes? There are several possibilities. It is likely that at least part of the benefit of total androgen blockade is due to blocking of the flare effect. This benefit would not be seen with orchiectomy. In addition, it may be that compliance with daily luteinizing hormone-releasing hormone (LHRH) injections was poor. If so, it is possible that patients who frequently missed injections would have frequent minor spikes in testosterone. In that case, the use of flutamide would have blocked the repeated "mini-flares," and thus produced a durable survival benefit. This would not be an issue in patients on long-term depot LHRH analog.

These studies have contributed enormously to the quality of evidence relating to the treatment of metastatic disease. It is safe to say that the magnitude of the effect of total androgen blockade is small; when orchiectomy is used, that effect appears to be negligible.

Unfortunately, some issues remain unresolved. What is the significance of the finding in the LHRH-flutamide study of an increased benefit in the patients with minimal metastatic disease? Does this mean there is a subset of patients who might benefit after all? Can these individuals be
identified using genetic markers, for example? What if flutamide had been stopped once biochemical progression occurred? What about biochemical failure following initial radical therapy, the most common current indication for the initiation of therapy? All of these questions will require further studies.

Intermittent vs Continuous Androgen Therapy
The second study reviewed, SWOG 9346, compares intermittent androgen deprivation (IAD) to continuous therapy. Intermittent androgen ablation, first reported in 1986,[3] offers undisputed benefits relative to quality of life (QOL) during the interval off treatment. Such therapy also may have potential benefits in terms of time to androgen independence and survival. Moreover, intermittent androgen deprivation reduces cost compared to continuous medical castration. The difficulty this trial has encountered is due to the stage migration effect of prostate-specific antigen (PSA) screening and monitoring. The number of newly diagnosed cases of stage D2 prostate cancer has dropped dramatically. In addition, patients who do not respond to radical therapy tend to be treated when their PSA rises, and therefore, are not candidates for a study of hormonally naive D2 disease.

Interestingly, the Medical Research Council (MRC) recently published the results of a trial of immediate vs deferred treatment for advanced prostate cancer. This was a randomized study of 938 patients with locally advanced or asymptomatic metastatic disease.[4] Both overall and disease-specific survival were improved in the immediate-treatment group.

Based on the MRC trial and general international trends, one can expect that patients will be treated progressively earlier with androgen ablation. Therefore, the appeal of intermittent androgen suppression for patients who have biochemical relapse is compelling. The SWOG 9346 trial will be an important contribution to our understanding of intermittent androgen suppression.

Adjuvant Radiotherapy vs Observation
The SWOG 8794 study of adjuvant radiotherapy vs observation following radical prostatectomy in patients with positive margins represents a tremendous accomplishment. This study addressed a mounting demographic problem, ie, the management of the patient with positive margins after radical prostatectomy. Phase 2 trials have suggested improved rates of local control in patients who receive adjuvant radiation.[5,6] In the absence of a comparative trial, no conclusions could be reached about the impact of this therapy on disease-specific survival. The SWOG trial was broad-based, and included the National Cancer Institute of Canada and other cooperative groups. The study nearly closed for lack of accrual on several occasions. A concerted effort by senior trial investigators to promote and publicize the trial, and to bring in contributors throughout North America, resulted in its eventual successful accrual.

This study, perhaps more than any other, illustrates the importance of cooperative clinical trials groups in furthering our ability to practice evidence-based medicine. This trial was hard to sell to patients. It required a concerted effort on the part of hundreds of physicians. The per-case funding for the trial was small. The motivation to accrue came largely from a desire by participants to answer this important scientific question. The results of this trial (to which accrual closed in December 1996) will have a major effect on the management of patients with positive margins.

This willingness to tackle the compelling but difficult scientific question also characterizes the Prostate Cancer Prevention Trial (PCPT) and the Prostate Intervention Versus Observation Trial (PIVOT). Regardless of their outcome, these trials will influence our understanding of prostate cancer and patient management for decades and possibly centuries to come.

The ability of the cooperative clinical trials groups to fund large difficult trials like the adjuvant radiation trial has been traditionally based on the funds provided by simpler pharmaceutical company-funded trials. Increasingly, these simpler trials are being funded outside of the cooperative clinical trials group infrastructure. One sincerely hopes that the SWOG 8794 adjuvant radiation trial will serve as an example to funding agencies of the importance of maintaining organizations that are willing and able to tackle the tough scientific questions in oncology, whether or not they are of interest to the pharmaceutical industry.

The GU Global Group
Another noteworthy SWOG accomplishment is the development of the GU Global Group. This group has facilitated the development of intergroup trials in a number of areas. The members of the global group represent thousands of clinicians with an interest in accruing patients into clinical trials. These physicians, in turn, have access to hundreds of thousands of patients who could potentially be accrued. The potential is enormous. The Global GU Group was instrumental in spearheading the intergroup collaboration that resulted in the successful completion of the adjuvant radiation trial for positive margins.
We are in the era of evidence-based medicine. SWOG represents a model for clinical trials that has been very successful. SWOG trials have addressed, and ultimately will answer, some of the most vexing questions in urologic oncology. As is often the case with good trials, some of the SWOG trials have raised more questions than they have answered. Given the prevalence of prostate cancer, and the societal costs, there is no excuse for not carrying out large randomized trials to address the fundamental questions that clinicians face. Most physicians who care for patients with prostate cancer are tired of telling patients, "We don't know the answer to that question," in response to most specific inquiries. The uncertainty has gone on long enough. It is time to get some answers. This will require a great deal of resources and the efficient functioning of large cooperative clinical trials groups, of which SWOG is emblematic.

References:


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