Ocular Oncology and the Study of Rare Cancers

The seven papers in this issue of Cancer Control deal with six different types of neoplasms of the eye and orbit: choroidal melanoma, retinoblastoma, primary ocular lymphoma, conjunctival melanoma, orbital rhabdomyosarcoma, and orbital meningioma. These tumors all have an obvious anatomic relationship to the anterior visual pathway, yet each has a different histogenesis, clinical presentation, pathology, and prognosis for vision and life. Despite their differences, these tumors share one important feature: they are all uncommon, if not rare conditions. The American Cancer Society estimated that approximately 2,200 new cases of all types of primary ocular and orbital malignancy were diagnosed in the United States in 2002, based on incidence rates from the Surveillance, Epidemiology and End Results Program of the National Cancer Institute. Uveal melanoma is the single most common malignancy of the eye and orbit and makes up nearly 70% of all malignancies of these tissues, or about 1,600 new cases each year. By comparison, the age-adjusted incidence of cutaneous melanoma alone is 20 times greater than that of all types of ocular and orbital cancer combined.

In an era when physicians and patients rely on evidence-based medicine to guide them in clinical decision making, uncommon cancers present challenging problems in how to design and conduct clinical trials. Until relatively recently, essentially all clinical decisions about the effectiveness of therapies for ocular cancer were based on retrospective series or single-armed studies with historical controls. The superiority of randomized clinical trials in determining effectiveness of new treatments is well established, but when dealing with uncommon conditions it may not be possible to recruit enough patients into a study to have sufficient statistical power to detect a treatment effect. In cancer trials, the dilemma is more perplexing because even a small risk reduction in the primary outcome of death is important to validate. The detection of a small treatment effect, however, requires enrollment of large numbers of patients, which is not realistic for most ocular cancers.

Further complicating the assessment of treatment of ocular cancer is the real possibility that therapy itself will result in loss of vision or loss of an eye. Investigators have found that vision-related quality of life assessment is another measure of clinical outcome that may be just as important as other traditional measurements, including longevity of life. Clinical trialists are now developing and validating tools that can reliably determine the impact of ocular cancer and its therapy on quality of life with respect to visual function, concerns about recurrence of cancer, and body image.

What options do ocular oncologists have for testing the effectiveness of therapies? The recruitment of patients into an underpowered clinical trial has been criticized as being unethical because it forces patients to relinquish their right to select therapy when the results of the study may be inconclusive. There are strong moralistic arguments in favor of underpowered clinical trials for rare diseases, however, given certain provisions. First, it would need to be acknowledged that the results of an underpowered study will be used in combination with similar studies to estimate treatment efficacy. This means that any such study be meticulously designed and conducted and thoroughly reported for future meta-analysis, standards that many randomized clinical trials to not currently meet. Second, investigators must fully inform potential enrollees that their participation may only indirectly contribute to the benefits of other patients. There are now improved statistical methods for combining data from underpowered trials that more fully exploit the potential of small studies.

Other options would be to maximize participation in clinical trials by increasing patient recruitment and to devise more efficient methods for developing and implementing cancer studies. How might such goals be reached? One approach to achieving both objectives is through the networking of large numbers of ocular oncologists using the Internet. While the concept of “networking” clinical centers for randomized clinical trial is not new, their linkage through the Internet is a relatively recent development.

Creating a consortium of this type is time-consuming and costly, but once established, the long-term dividends would be great. Internet communication makes possible the rapid and secure transmission of patient eligibility evaluations, baseline and follow-up eye examinations, intervention allocations, standardized data collection, data monitors, and quality control monitors. The training and certification of participating technologists, nurses, and physicians can often be accomplished over the Internet, as can the reporting of adverse effects. Most importantly, once the infrastructure for performing a clinical trial has
been set up, the development and implementation of new protocols become increasingly more efficient. Networking a large number of ocular oncologists in North America, or even internationally, for the collaboration of clinical studies is both feasible and inevitable, given the direction that information technology is moving. Internet-linked research consortia like the Pediatric Eye Disease Investigator Group have already enjoyed considerable success.8,9 The ability to test new therapies for rare cancers like those of the eye and orbit would be advanced by a permanent consortium of Internet-linked university-based and private practice-based oncologists.

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References