Reflections on Medical Oncology: 25 Years of Clinical Trials—Where Have We Come and Where Are We Going?

Christopher M. Booth, National Cancer Institute of Canada Clinical Trials Group, Queen’s University, Kingston, Ontario, Canada
Ian Tannock, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada

Twenty-five years ago in the first issue of Journal of Clinical Oncology, Tannock and Murphy1 appealed for better design and improved reporting of clinical trials in oncology, and proposed five areas in which journals and investigators could improve the quality of clinical cancer research. As shown in Figure 1, these recommendations pertain to three inter-related themes: appropriate design and size of trials, the selection of clinically relevant end points, and reporting that is free of bias. In this Silver Anniversary issue, we reflect on how well the evolution of clinical trials has adhered to these principles during the last 25 years.

### APPROPRIATE DESIGN OF CLINICAL TRIALS

The paradigm of drug development in oncology from phase I (clinical pharmacology and toxicity) to phase II (initial investigation of activity) to phase III trials (comparative evaluation of clinical benefit) remains largely unaltered since 1983. As described in the initial article,1 the conduct of countless small single-arm clinical trials is not an efficient use of patient or financial resources. Unfortunately, this problem persists.2 Recently, our group determined the proportion of positive phase II trials that proceed to phase III evaluation. Among phase II trials reporting promising activity of a new treatment in 1995 to 1996, only 13% were followed by a phase III study. A survey of authors reporting positive phase II studies in 2006 indicates that this proportion is unlikely to increase. Reasons for this include lack of patient and financial resources, and limited access to the drug(s).3 Phase II trials should be planned such that new treatments with promising activity are compared subsequently with standard treatment in a randomized controlled trial (RCT). Unfortunately, most phase II trials are not initiated as part of this planned sequence: rather they are used to justify use of a nonstandard treatment, and resources spent on them would be better applied to RCTs that have the potential to change practice.

The publication of guidelines for the appropriate design, analysis, and reporting of clinical trials, such as the CONSORT statement,4 has had a positive influence on the quality of clinical research, but fundamental deficiencies persist. A review of abstracts describing RCTs presented at American Society of Clinical Oncology (ASCO) Annual Meetings (1989 to 1998) found that only 22% of studies explicitly identified the primary end point.5 In an overview of reports of 326 RCTs in breast, colorectal, and non–small-cell lung cancers published between 1975 and 2004, only about two thirds of published studies clearly identified the primary end point, even in the most recent decade, and there was heterogeneity in the use and definition of intention to treat analysis.6 An overview of RCTs for patients with primary brain tumors found evidence of improved reporting between 1990 and 2004, but key variables such as concealment of randomization, blinding, and adherence to intention to treat principles were reported in less than 30% of articles.7 In their review of 423 RCTs presented at ASCO Annual Meetings in 1995 to 2003, Bedard et al8 found that 57% of studies did not have adequate power to detect even a medium-sized treatment effect. However, phase III trials have become progressively larger over time.6,9

### CLINICALLY RELEVANT END POINTS

Most patients (and their oncologists) would define a useful therapy as one that increases survival or provides palliative benefit through reduction of cancer-related symptoms and improved quality of life (QOL). Tumor response or reduction in serum level of a tumor marker may indicate biologic activity of a new treatment, but these are not measures of benefit to patients. Therefore, it is reassuring that there has been increasing use of survival and decreasing use of response rate as the primary end point in phase III studies.6 End points that reflect clinical benefit have sometimes led to new standards of care. The pivotal trial comparing gemcitabine versus fluorouracil in patients with advanced pancreatic cancer demonstrated improvement in the primary end point of clinical benefit (a composite of pain, performance status, and weight), thereby changing the standard of care, despite a minimal increase in survival.10 Unfortunately, the term “clinical benefit” is sometimes misused to describe the patients enrolled onto a trial who have either tumor shrinkage or stable disease11; whether such patients have true clinical benefit (in the lay sense) will depend on whether they also have improvement in the duration or quality of survival.

Patient-reported outcomes are used increasingly as secondary end points in contemporary clinical trials. For example, the TAX 327 trial, which compared docetaxel versus mitoxantrone for men with
hormone-refractory prostate cancer, found a modest improvement in median survival (about 3 months) with the use of docetaxel administered once every 3 weeks, but parallel improvements in pain and QOL support the widespread adoption of this therapy. Unfortunately, current standards for analyzing QOL and symptom control are generally poor. In a review of 112 RCTs for advanced cancer, Joly et al found that only 19% of studies established an a priori hypothesis relevant to palliation, and 21% defined minimal differences in QOL and symptom scores that were clinically meaningful. Furthermore, most trials reported changes in a median or mean QOL score, which is rather like defining tumor response by the change in tumor volume averaged over a group of patients. Few studies used the preferred method of describing the proportion of patients who satisfied a predefined criterion for improved QOL or symptom control.

The encouraging trend toward use of clinically relevant end points has been tempered by pressure on investigators to choose primary end points that expedite the translation of research findings into practice. Accordingly, many contemporary RCTs use primary end points, which are believed to be surrogates for overall survival, such as disease-free survival (DFS) or time to progression. A potential pitfall of this trend is that new regimens become established in clinical practice before it is determined whether they provide true benefit. If surrogate end points are to be used, it is critical that they correlate with overall survival. Disease-free survival at 3 years was well correlated with overall survival in 20,898 patients treated with adjuvant therapy for colon cancer. A similar relationship is often assumed in trials of adjuvant therapy for breast cancer, and large early differences in DFS generally translate into subsequent smaller differences in overall survival. However, there is no inherent reason that early gains in DFS obtained with a new treatment will lead to improvement in overall survival, given that there might be an equal effect on survival by applying the new treatment after relapse. Thus, small early differences in absolute DFS in clinical trials comparing adjuvant use of aromatase inhibitors with tamoxifen, such as in the Arimidex, Tamoxifen, Alone or in Combination trial, might or might not lead to later gains in survival.

The reporting of clinical trials is subject to bias, including the selective reporting of trials with apparently significant results (publication bias) and the association between trial sponsorship and study results (sponsorship bias). A survey of 510 abstracts presented at annual ASCO Annual Meetings (1989 to 1998) found that 26% of RCTs were not published in full within 5 years of presentation. Eighty-one percent of studies with significant results had been published by this time, compared with 68% of studies with nonsignificant results (P < .01). Nonpublication breaks the contract that investigators make with trial participants, funding agencies, and ethics boards. The current
requirement to register clinical trials at their inception should encourage the reporting of all of them, regardless of their results.

Commercial sponsorship of trials has been associated with reporting of positive results. For example, of RCTs evaluating treatments for myeloma published between 1996 and 1998, 47% of those funded by nonprofit organizations favored the experimental arm compared with 74% of studies funded by industry, and parallel results have been reported for breast cancer and other sites. In our overview of 326 RCTs published between 1975 and 2004, there was a 10-fold increase in industry sponsorship over time and a strong association between for-profit sponsorship and endorsement of the experimental arm.

In the last 25 years, substantial advances in clinical oncology have occurred based on the findings of well-designed RCTs. The molecular era of cancer therapeutics has introduced new challenges to the design of clinical trials, and correlative science has generated biomarkers that are used as end points in early-phase studies and RCTs. However, the primary goal of any treatment remains the same: to allow patients to live longer or to live better. As for trials of chemotherapy, it is essential to establish the relationship between these surrogate end points and those that reflect benefit to patients.

Increased effort is required to understand how the results of RCTs influence clinical practice and to assess the benefit of new treatments in the general population. Although they are usually omitted from the hierarchy of studies considered in evidence-based medicine, population-based outcome studies can provide valuable information regarding the true benefit of novel therapies. In addition, all health care systems have limited resources, so that pharmacoeconomic analyses should complement those of efficacy and toxicity to provide insight into which treatments offer the greatest societal benefit. Finally, it is critical for investigators, clinicians, and policy-makers to retain and refine perspective on what constitutes a meaningful benefit regarding the true benefit of novel therapies. In addition, all health population-based outcome studies can provide valuable information from the hierarchy of studies considered in evidence-based medicine, phase III studies. J Clin Oncol 25:325s, 2007 (suppl; abstr 6514)


Ng RC, Pond GR, Tang PA, et al: Correlation between changes in 2- or 3-year disease-free survival (DFS) and 5-year overall survival (OS) in adjuvant breast cancer trials from 1966-2006. J Clin Oncol 25:225s, 2007 (suppl; abstr 581)


Krzyzanowska MK, Pintilie M, Tannock IF: Factors associated with failure to publish large randomized trials presented at an oncology meeting. JAMA 290:499-501, 2003


REFERENCES


15. Ng RC, Pond GR, Tang PA, et al: Correlation between changes in 2- or 3-year disease-free survival (DFS) and 5-year overall survival (OS) in adjuvant breast cancer trials from 1966-2006. J Clin Oncol 25:225s, 2007 (suppl; abstr 581)


