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EDITORIAL

In and Out, Good and Bad News, of Generalizability of SWOG Treatment Trial Results

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The issue of generalizability of clinical trial results has challenged researchers and practitioners of adult cancer patients for years. It is one reason why the adult cancer cooperative group enterprise in the United States is undergoing yet another transformation (1).

Figure 1 may capture the essence of the situation. Its foreground shows the most recent data available to this commentator on the estimated proportion of cancer patients in the United States entered onto cooperative group treatment trials as a function of individual year of patient age. The background shows the rest of the United States. With only 2% to 4% of adults aged 20 to 65 years entered onto clinical trials, how can we rely on such a small sample size to be applicable to the general population?

In a comparison of survival outcomes among cancer patients treated in and out of clinical trials published in this issue of the Journal, Unger and colleagues analyzed 21 SWOG treatment trials enrolled during the period from 1986 to 2007 with comparable patients in the US Surveillance, Epidemiology and End Results (SEER) database (2). Their primary subset analysis was good- vs poor-prognosis trials defined by a 2-year average study-specific survival rate of greater than 50% or less than or equal to 50%, respectively. The former had 11 trials that included melanoma, myeloma, and carcinoma of the breast, bladder, uterine cervix, and prostate. The latter had 10 trials that included acute myelogenous leukemia, brain tumors, lung cancer, and pancreatic carcinoma.

The results may be interpreted as a series of good- vs bad-news scenarios (Table 1), with several advantages as a source of disadvantage and vice versa. Among the best news is that patients in SWOG trials had a survival benefit, albeit only in poor-prognosis trials. The bad news for them was that it "endured for only 1 year" (2). However, according to Supplementary Figure 2 in the Unger et al. report (2), which shows the SWOG and SEER survival curves for each of 10 poor-prognosis trials, the survival benefit is better than the authors concluded, lasting at least 5 years in two trials, 3 years in three trials, and 2 years in two trials. In only two of the 10 trials was it less than 1 year.

Whether or not the apparent benefit of the SWOG trial in patients with a poor prognosis is more durable than concluded, the striking difference between the broad categories of good and poor prognosis as defined has major implications for the interpretation of cancer clinical trial outcomes and application to the general population:

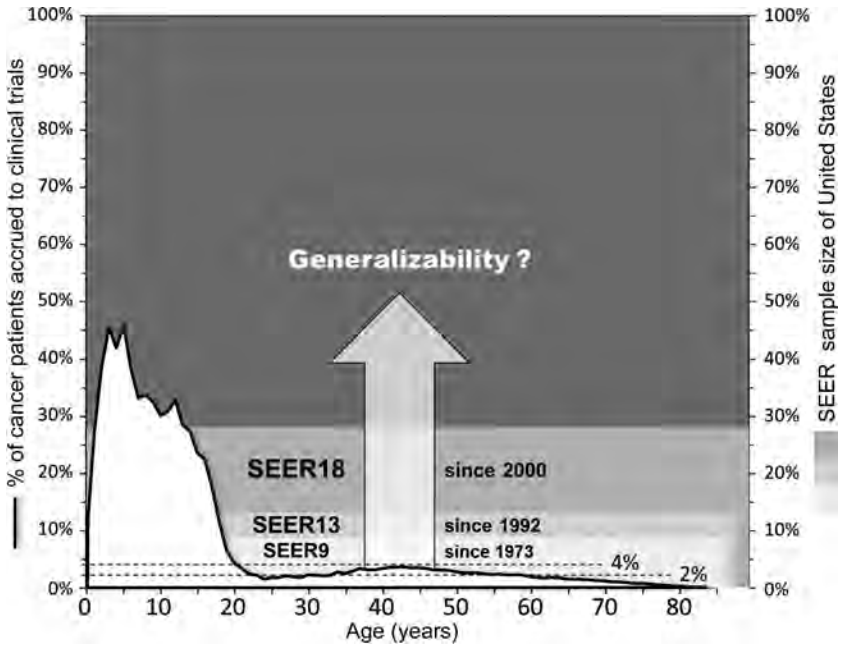

Figure 1. Estimated National Cooperative Group Clinical Trial accrual proportion ofpatients diagnosed with cancer during the period from 2008 to 2010 by single year of age. SEER = Surveillance, Epidemiology, and End Results. Data from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, courtesy of Nita Seibel, Steve Friedman, Mike Montello, and Shanda Finnegan.

Table 1. Good-news and bad-news scenarios of the SWOG clinical trials and Surveillance, Epidemiology, and End Results (SEER) survival comparisons

Good news	Bad news
Good-prognosis trial results translate to the real world setting; at least for SWOG studies, a generalizability has not been as apparent in prior reviews (3,4).	Poor-prognosis SWOG trial results are not applicable to the comparable general cancer population (because most of them had substantially better survival than comparable SEER patients).
Community oncologists have even more evidence to refer poor-prognosis patients to centers conducting clinical trials in that disease.	For overall national improvement, the poor-prognosis group should be more generalizable than the good-prognosis group.
For the patients themselves in trials of poor-prognosis cancers, they had a chance of better survival, whether it was due to the Hawthorne effect (5), from care administered according to strict protocol (6), or other factors not mentioned by the authors.	For the patients themselves in trials of poor-prognosis cancers, the survival benefit lasted, according to the authors, for only 1 year.
Hispanics and blacks had overall survival benefits similar to the general population.	Hispanics and blacks had survival compromise similar to the general population.
Eligibility criteria for entry onto cancer clinical trials were once again (7) found to be too strict, especially for patients with a poor prognosis.	The future of trials in cancer patients will require, in most cases, narrowing eligibility criteria as more new agents with specific molecular targets become available and will be applicable to fewer patients. The era of large clinical trials is waning.
Broadening eligibility criteria will enable more patients to participate in clinical trials.	

1. The clinical trials in patients with a poor prognosis are optimistic, with survival benefits that do not, in general, last much beyond a couple of years.
2. Bad cancers are being studied in clinical trials in ways that are of limited help to oncologists taking care of patients who do not participate in clinical trials.
3. Patients not entered onto clinical trials are older and/or have more coexisting morbidities.
4. Eligibility criteria for entry onto cancer clinical trials are too strict, especially for patients with a poor prognosis.

Limitations of the study that are directly described by the authors include: 1) treatment per se could not be assessed in SEER patients, 2) SWOG and SEER groups had different endpoint assessments, and 3) SEER patients tend to be of higher socioeconomic status (SES) than the general population (8,9). The SES difference was countered by the authors in noting that patients who participate in cancer clinical trials are generally also of higher SES. A limitation indirectly discussed was that the outcome of the standard-of-therapy control regimens in their trials could not be compared with the SEER results. Not discussed was the possibility of more harms from newer therapies tested, which, given the increasing recognition of the importance of quality-of-life survival (10–13) and toxicities and financial cost of newer therapies (11,14,15), is unfortunate.

The issue of SEER generalizability (Figure 1) was also understated. The control group for each of the 21 SWOG trials required that the corresponding SEER patients had a diagnosis date during the SWOG study's enrollment period. Only four of the 21 studies were conducted during the years of SEER18 and its 28% sample size (Figure 1) and more representative racial/ethnic and SES balance (16,17). The appropriate controls for the 17 studies that were conducted during the period from 1987 to 1999 are SEER9 and SEER13 for the years 1981 to 1991 and 1992 to 1999, respectively, which represented only 9.5% and 13% of the country, respectively (Figure 1) (17). Of the 4295 patients enrolled on the 21 SEER studies, 83% were enrolled when SEER9 and SEER13 were the control groups, compromising an estimate of generalizability of trials conducted a quarter century ago.

Finally, as highlighted in Figure 1 and lauded in an editorial by the health services researchers at the Mount Sinai School of Medicine and Mayo Clinic (18), the high rate of clinical trial participation in the United States of children and adolescents with cancer onto Children's Oncology Group (COG) trials should be cited. As stated in the editorial, COG includes more than 5000 US pediatric cancer specialists taking care of 90% of US children with cancer who receive care in centers affiliated with this network (18). The robust clinical trial enterprise for this patient population offers a model for improving outcomes in other age groups and populations, which, hopefully, the new National Clinical Trials Network (1) can apply.

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Notes

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