

Completion Rates of Adjuvant Chemotherapy for Colon Cancer: A Historical Perspective

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The impact of adjuvant therapy on cancer survival is one of our most important recent achievements in medical oncology. This milestone has been accomplished through the use of clinical trials especially among patients with breast and colon cancer. The annual odds of death from breast cancer alone among patients in these trials has decreased by up to 28%, depending on the criteria used for patient enrollment, the types of treatment given, and the characteristics of the tumors themselves (1). Similar, but less well-defined, results have been reported for colon cancer (2–5).

Randomized clinical trials provide us with the strongest evidence of efficacy for adjuvant cancer treatments. Observational studies such as that of Dobie et al. (6) in this issue of the *Journal* provide information on the long-term effectiveness of adjuvant treatments among a population-based sample. They indicate which factors predict the receipt of appropriate treatment, long-term overall and cancer-specific survival, and the adverse events that may accompany such therapy.

The Surveillance, Epidemiology, and End-results (SEER) database was developed by combining regional cancer registries. Thanks to the work of Potosky et al. (7), both the SEER and Medicare databases were linked in 1993. Now researchers have been provided with the tools to not only assess the use of surgical and radiation treatments among elderly cancer patients but also measure the use of adjuvant chemotherapy and the factors that predict whether it is given (7–9). Today, SEER collects information from 14 population-based and three supplemental cancer registries covering 26% of the U.S. population, including many belonging to minority groups and to underserved groups (6).

Using 1992–1996 SEER program data linked to 1991–1998 Medicare claims, Dobie et al. (6) set out to examine the completion rate of adjuvant chemotherapy for colon cancer and its consequences in this elderly population. The number of patients who fulfilled study criteria for analyzable data was 5778 of a total of 9796 patients who were identified as being aged 66 years or older and had primary stage III colon cancer diagnosed between January 1, 1992, and December 31, 1996. The findings are worthy of comment and should add to the education of medical oncologists and other physicians who participate in the management of patients undergoing curative resections for colon cancer. The effects of sex, age, factors related to social support (e.g., marital status), and ethnicity on completion rates are particularly noteworthy. Tumor characteristics, annual household income, and SEER region were not statistically independent predictors of adjuvant chemotherapy completion. Before commenting on the findings, however, we want to expand on the historical perspective of this adjuvant chemotherapy period selected by the investigators.

In 1990, Intergroup investigators (10) confirmed the results of a smaller Mayo Clinic–initiated randomized study (11) that provided evidence for the value of a 1-year treatment with 5-fluorouracil (5FU) and levamisole as adjuvant chemotherapy for colon cancer. The importance of these findings after more than two decades of negative 5FU adjuvant studies was underscored

by a 1990 National Institutes of Health Consensus Development Conference on Colorectal Cancer (12). When informed of the data from these two trials, oncologists readily adopted the use of adjuvant chemotherapy despite the controversy about the role of levamisole and its price [a subject that led to lively correspondence in the *New England Journal of Medicine* (13,14) and in comments at various meetings including a plenary session of the American Society for Clinical Oncology in 1991 by the late Charles Moertel]. Clinical trials explored the role of 5FU and leucovorin in comparison with the more toxic combination of 5FU and levamisole, and treatment cycle was shortened to 6 months (3). The shorter cycle proved adequate, and this adjuvant therapy became the standard until the superiority of oxaliplatin-containing regimens was established, as shown by the results from the recently published MOSAIC trial (15). The period chosen for analysis of the present study included this transition to a 6-month course of treatment, and the authors appropriately defined a complete course as anybody who had received at least 5 months of treatment. However, it is possible that the 1-year course and the lack of tolerance of levamisole discouraged adjuvant treatment of elderly patients during this period. The greater percentage of patients initiating adjuvant therapy in 1996 (60.4%) than in 1992 (53.8%) may be indicative of both the less daunting adjuvant treatment in later years and the lag time for its acceptance by oncologists.

What do the analyses of patient characteristics tell us about providing early termination of adjuvant chemotherapy? The importance of this inquiry lies not only in its impact on outcomes but also in its possible elucidation of factors that contribute to decision making by oncologists and patients. For example, the striking finding of poor completion of adjuvant therapy among women gives rise to a variety of possible hypotheses: from poor tolerance of the agent, to sex-related attitudes toward treatment, to less social support when the female spouse is ill than when the male is ill. The analysis also brings into sharp focus an issue of increasing importance—the effect of age.

The investigators have done an outstanding job in collating and analyzing their data. Unfortunately, as they recognize, limitations exist in relating Medicare claims data to clinically relevant phenomena; e.g., 1 day of chemotherapy each month for 6 months may not provide the entire story of chemotherapy completion. Likewise, the database contains no information about actual dose given and toxicity. We know little about other factors

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that interfere with completion of therapy such as a patient's literacy, the severity of an individual's comorbidities, quality of life and functional status, or a patient's unique (rather than average census tract) socioeconomic data. Also, women who drop out may do so because of the frailty of old age rather than other more remedial causes.

So what is the take-home message? The investigators have confirmed the merits of patients and physicians carefully following complete treatment schedules of adjuvant chemotherapy trials. They showed that duration of treatment may be critical to achieve optimal survival outcomes. As they point out, however, prospective studies are still required to assess the predictors of completing treatment that can be found in analyzing SEER–Medicare data. Such studies are under way for breast cancer, but more studies are needed for newly diagnosed colon cancer. Collection of prospective data will go a long way in elucidating decision making by both physicians and patients that can validate the intriguing findings of this well-done study.

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