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Breast Cancer and Chemotherapy

In her article of 12 March (News and Comment, p. 1029), Barbara J. Culliton discusses a study by Bonadonna *et al.* (*1*), in which chemotherapy was used as an adjuvant to radical mastectomy, and criticizes as "greatly exaggerated" my characterization of the study as a work of "monumental importance" (*2*).

Appearance of clinically manifest breast cancer after the initial resection predictably leads to death despite temporary remission. Axillary node metastases at the time of mastectomy are sentinel lesions indicative of a high probability of micrometastases in other body sites. Without chemotherapy, only 23.9 percent of 163 women with one or more positive axillary nodes and 13.8 percent of 87 women with four or more positive nodes at the time of surgery were alive 10 years later (*3*).

Modeling from combination chemotherapy of acute leukemia, Cooper (*4*) described a chemotherapeutic program for metastatic breast cancer using five drugs—vincristine (V), prednisone (P), cyclophosphamide (C), methotrexate (M), and 5-fluorouracil (F). In terms of remission induction, this regimen was superior to any single drug therapy previously employed; nonetheless, half the patients in a group treated with the five-drug therapy were dead in 1 year and 75 percent in 2 years (*5*). Others studied components of Cooper's five-drug regimen by omitting one or two drugs. A three-drug combination (CMF) was found more effective than a single oral drug, L-phenylalanine mustard (L-PAM), in suppressing metastatic breast cancer (*6*). Both treatments were then tested immediately after surgery in women who had axillary node metastases. The L-PAM study, conducted in the United States, was published (*7*) as a report of early findings at a time when significant delay in appearance of recrudescent cancer ($P = 0.2$) was seen only in premenopausal women.

Bonadonna *et al.* (*1*) reported a controlled, randomized trial in 386 women in which 12 monthly courses of CMF were administered to one group after surgery; a control group received no postoperative treatment. After 27 months, there were 11 relapses in 207 patients (5.3 percent) in the CMF group and 43 in 179 patients (24.0 percent) in the control group ($P = < .000001$). Furthermore, CMF was significantly superior for patients in *every* subset of the study classified by age, ovarian function, number of nodes involved, and extent of mastectomy. This was also true for the 90 percent of patients with the commonest pathologic type of tumor and the 89 percent whose tumors were more than 2 centimeters in diameter. Bonadonna *et al.* presented their relapse data in the form of life-table plots, the most effective way to describe the events that occurred. These events, in turn, give the best indication of how the entire group, of which the early members are a subset, will behave. Treatment failure distributions after 27 months were projected to be 10 percent for the CMF group and 43 percent for the control group ($P = .00002$). No patient treated with the full CMF regimen had relapsed after the drug therapy was ended. For the subset of 122 patients with the worst prognosis—those with four or more metastatic nodes—the projected treatment failures by life-table plot are 19 percent for the CMF group and 76 percent for the control group ($P = .001$). All relapsed patients are expected to die. Like many experimental neoplasms, disseminated human cancer can in some instances be cured by drugs when micrometastatic, but rarely when clinically evident. This principle, adopted from experience with experimental and clinical acute leukemia, has also been demonstrated in Wilm's tumor, osteogenic sarcoma, embryonal rhabdomyosarcoma, Ewing's tumor, and Hodgkin's disease. The Italian data and the experience with micrometastatic cancer as a biologic phenomenon rather than a unique characteristic of breast cancer support the proposition that some patients in the CMF treatment group have been cured. Mortality data after 32 months show a difference: 11 of 179 patients in the control group have died, compared with only 4 of the 207 patients treated with CMF ($P = .03$) (*8*).

Culliton and Costanza (*9*) assert that postoperative chemotherapy is still an experimental method not to be undertaken outside the research setting because of unknown late effects. The drugs have been in use singly for 18 years or more, and in combination for half that time. The risks are reasonably well un-

derstood. The late effects of the disease are also well known and are worse. At current rates some 89,000 women will develop breast cancer this year in the United States alone. It is expected that, of these, 47 percent will have axillary metastases (*10*). These 42,000 women in 1 year cannot all go to the approximately 200 university hospitals and research institutions in the country. As many as can should, so the absolute therapy may some day be found. But emotional, economic, and logistic considerations preclude this option for the majority. What use biostatisticians if an important, beneficial finding that could have occurred by chance only twice in 100,000 times (or once in a million) is denied to the women in Anyplace, U.S.A.? If there were delay for years of follow-up studies before adopting the therapy, 10,000 women every 4 months would be consigned to a course of inaction that leads to an early death from metastatic cancer. Women in these numbers could not conceivably succumb from adverse effects of the treatment. There were no drug deaths among Bonadonna's patients. Who makes the lag in translating research success into clinical practice?

I advocated and advocate research, but wrote (*2*) that its impossibility for most patients should not impede adoption of this treatment by *qualified* physicians. This adjective appears to have gone unappreciated; 727 certified internists have already been further certified by the American Board of Internal Medicine in the subspecialty of medical oncology (*11*). Hundreds of other physicians are experienced in the use of these drugs in patients with advanced, clinically manifest breast cancer, where the chance for cure approaches zero.

Bonadonna's study has demonstrated the effectiveness of CMF in controlling local recurrence of metastases on the chest wall (there have been three recurrences in the CMF group of 207 patients and 11 in the control group of 179 patients) and in bringing about improved remission and survival rates after 27 months. One might hope the use of adjuvant postoperative radiotherapy for breast cancer—long-entrenched and widely used, but with no evidence of survival benefits (*12*)—would cease and give way to chemotherapy (*13*). Cullitton expresses apprehension about sterility from chemotherapy for breast cancer, a virtual nonissue. Dead women tell no tales, nursery or otherwise. Furthermore, less than 20 percent of women with breast cancer are under age 45 (*10*).

After developing his regimen, Cooper treated in adjuvant fashion 100 women with breast cancer with four or more metastatic axillary lymph nodes. Of these, 73 were treated with VPCMF for the 9 months immediately after radical mastectomy. By life-table plot, 70 percent of them are alive without evidence of disease after 8 years, a phenomenon strikingly different from Bonadonna's control patients but not dissimilar, during the initial portion of the curve, from his CMF patients (*14*). These data should also be compared to historical precedents: of 14,294 women with one or more positive nodes, 58 percent were dead in 8 years (*10*); of 88 women with four or more positive nodes, 81 percent were dead in 8 years (*3*).

A delicate balance exists between making available today's research achievements in the practice of medicine and the conduct of ongoing clinical research to attain the ultimate objective. The ethics of the clinical investigator of breast cancer are concerned not only with today's victims; he must serve as steward for future millions the world over who will die of breast cancer each decade until prevention or cure becomes a reality for all. Salvage of the breast should remain a secondary goal until salvage of the patient is firmly assured. The appearance of these chemotherapeutic data (*1, 7, 14*), however, which prove the feasibility of an approach to the real problem of breast cancer, micrometastatic disease, is of more significance for today's patient than any other therapeutic advance in breast cancer since the modern era of breast cancer surgery began before the turn of the century.

JAMES F. HOLLAND

Department of Neoplastic Diseases, Mount Sinai School of Medicine, New York 10029

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