

Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnattelli L, Brambilla C, De Lena M, Tancini G, Bajetta E, Musumeci R & Veronesi U. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N. Engl. J. Med.* 294:405-10, 1976. [Istituto Nazionale Tumori, Milan, Italy]

The paper reports the significantly increased relapse-free survival in women with resectable breast cancer and histologically positive axillary nodes when postoperative combination chemotherapy (CMF) was randomly tested versus surgery alone. Most of the initial findings observed in 386 patients are now being confirmed at the 10-year analysis. [The *SCJ*® indicates that this paper has been cited in over 430 publications since 1976.]

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In May 1972, Paul P. Carbone invited me to visit the National Cancer Institute (NCI). During breakfast at 5:30 a.m., he began talking about new approaches to combination therapy for primary breast cancer. During the drive to NCI, he continued to discuss the treatment programs that the Breast Cancer Task Force was about to start. In his office, he showed me the annual report he had written a few months earlier when director of the Medicine Branch. It included the initial NCI data on a quadruple-drug regimen, CMFP, an acronym for cyclophosphamide, methotrexate, fluorouracil, and prednisone.

While Paul worked at his desk, I read the study protocol of the Eastern Cooperative Study Group (ECOG). The group was testing CMF versus PAM (phenylalanine mustard) in advanced breast cancer. I also read the first draft of the new National Surgical Adjuvant Breast Program (NSABP) trial on radical mastectomy versus radical mastectomy followed by adjuvant PAM. I asked Paul whether testing CMF chemotherapy as an adjuvant treatment would be worthwhile. He agreed and strongly advised me to design such a study by utilizing the large case series of breast cancer patients available in Milan. During the next few hours, I drafted two

CMF protocols, one for clinically advanced breast cancer and one for surgically resectable tumors with histologically positive axillary nodes. I got Paul's approval almost immediately—before noon—because the experimental design, including patient selection, stratification parameters, and follow-up evaluation, was almost superimposable on those of the NSABP trial. Last but not least, he lent his support to funding the studies through NCI.

At home, my proposal immediately met the approval of the director and the surgical staff of the Istituto Nazionale Tumori di Milan. We started our adjuvant study about a year later and conducted the entire project with women admitted to and treated at the institute.

The initial findings showed a statistical improvement in the relapse-free survival rates in women receiving multimodality therapy versus surgery alone. Publication of this study produced an unexpected explosive reaction among physicians and laymen because the results clearly suggested that prolonged adjuvant combination chemotherapy could alter the course of a common neoplasm that had almost always been regarded as a localized disease if found resectable by conventional means. Thus the study established not only the prevalent systemic nature of certain forms of primary breast cancer, but also the value of chemotherapy when combined with surgery. The trial results, which were largely confirmed by the 3-, 5-, and 10-year follow-up analyses,¹⁻⁴ continued for the subsequent decade to remain an important reference point for the numerous adjuvant studies that, following our first publication, were mounted all over the world. Last but not least, the experimental design and multidisciplinary cooperation of the study confirmed how powerful a tool the randomized clinical trial was as a research method, and substantially contributed to improving the lingering difficulties in crossing medical compartments.

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2. Rossi A, Bonadonna G, Valagussa P & Veronesi U. Multimodal treatment in operable breast cancer: five-year results of the CMF programme. *Brit. Med. J.* 282:1427-31, 1981.
3. Bonadonna G, Rossi A, Tancini G, Brambilla C & Valagussa P. Adjuvant chemotherapy trials in resectable breast cancer with positive axillary nodes. The experience of the Milan Cancer Institute. (Jones S E & Salmon S E, eds.) *Adjuvant therapy of cancer IV*. New York: Grune & Stratton, 1984. p. 195-208.
4. Bonadonna G, Valagussa P, Rossi A, Tancini G, Brambilla C, Zambetti M & Veronesi U. Ten-year follow up of adjuvant breast study. *Breast Cancer Res. Treat.* 5, 1985. (In press.)