CC/NUMBER 7
FEBRUARY 17, 1986

This Week's Citation Classic®

Schein P S, DeVita V T, Jr., Hubbard S, Chabner B A, Canellos G P, Berard C & Young R C. Bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma. *Ann. Intern. Med.* 85:417-22, 1976.
[Medicine Branch and Lab. Pathology, National Cancer Institute, Bethesda, MD]

In the past, diffuse large-cell non-Hodgkin's lymphoma (diffuse histiocytic lymphoma in previous terminology), typically presenting in advanced stage, was an almost invariably fatal disease. A new form of combination chemotherapy, described in this manuscript, was designed to combat the pattern of early relapse that thwarted efforts of tumor control with other regimens. The results of this trial confirmed that complete remissions with chemotherapy could not only be achieved, but that such responses are associated with long-term disease-free survival in most cases. [The SCI® indicates that this paper has been cited in over 225 publications since 1976.]

Philip S. Schein
Clinical Research and Development
Smith Kline & French Laboratories
Swedeland, PA 19479

January 20, 1986

The BACOP regimen for aggressive histologic forms of non-Hodgkin's lymphoma was designed while I was a senior investigator in the Medicine Branch of the National Cancer Institute. My coauthors on the manuscript were an extraordinary group of young, dynamic, and creative clinical investigators who were making many important contributions to the management of Hodgkin's disease as well as non-Hodgkin's lymphoma.

Vincent DeVita, now director of the National Cancer Institute, asked me to review the experience of the National Cancer Institute in the use of combination chemotherapy in the management of all forms of non-Hodgkin's lymphoma. This analysis, subsequently published in 1974,[1] demonstrated that combination chemotherapy patterned after the MOPP regimen of nitrogen mustard, vincristine, procarbazine, and prednisone could produce disease-free survival in cases with specific forms of advanced-stage non-Hodgkin's lymphoma.

Long-term benefit was largely confined to those patients with tumors of more aggressive histology, which were designated diffuse histiocytic lymphoma or, in more current terminology, diffuse large-cell lymphoma. This finding was regarded as very important since patients with advanced stages of this disease had had an almost invariably fatal course, with a median survival of six months. The majority succumbed to lymphoma within one year.[2] Patients who achieved only a partial response with the same therapy evidenced a deceptively favorable initial response, which was followed by rapid relapse of the lymphoma, usually during the rest periods between courses of therapy.

The BACOP regimen was designed to address this newly recognized pattern of relapse. Treatment during each 30-day course was divided into two phases. During the first two weeks of therapy, the lymphoma was treated with three potent anticancer agents including doxorubicin, which had only recently been recognized as an important agent for the mangement of diffuse histiocytic lymphoma. This was followed by two additional weeks of therapy with agents that were selected for their lack of bone marrow toxicity: bleomycin and prednisone. The patient thus received treatment for six full months. The intent was to prevent tumor regrowth between courses of treatment, while allowing for full bone marrow recovery.

The five-drug regimen was given the acronym BACOP, which not only served to describe the agents in the combination, but also the strategy we were evaluating. We were, in essence, "backing-up" the initial myelosuppressive phase of therapy with two additional agents in the second phase, in the hope of preventing tumor regrowth until the administration of the next phase of more potent drugs.

This latter goal was at least partially achieved. Approximately 50 percent of previously untreated patients with predominantly stage IV histiocytic-lymphocytic lymphoma evidenced a complete disappearance of their lymphoma. At the time of our report, this was the highest complete remission rate to be described in the literature.

The BACOP regimen has been largely superseded by the other forms of combination chemotherapy that have come into favor during the years. Whether any of the new regimens provide a significantly higher level of efficacy relative to BACOP is a subject of discussion. One of the problems that plagues this area of clinical investigation is the lack of properly designed controlled trials that compare therapies in patient groups with equivalent prognostic features.

The publication of our results with BACOP provided confirmatory evidence that complete remission in the aggressive forms of non-Hodgkin's lymphoma, of very advanced stage, could be achieved with combination chemotherapy. In addition, long-term disease-free survival, indeed cure, could be offered for what had in the past been regarded as an almost invariably fatal disease.

1. **Schein P S, Chabner B A, Canellos G P, Young R C, Berard C W & DeVita V T.** Potential for prolonged disease-free survival following combination chemotherapy of non-Hodgkin's lymphoma. *Blood* 43:181-9, 1974. (Cited 175 times.)

2. **Jones S E, Fuks Z, Bull M, Kadin M E, Dorfman R F, Kaplan H S, Rosenberg S A & Kim H.** Non-Hodgkin's lymphomas. IV. Clinicopathologic correlation in 405 cases. *Cancer* 31:806-23, 1973. (Cited 450 times.)

2-8