CORRESPONDENCE

Brief Weekly Chemotherapy for Elderly Patients With Intermediate-Grade or High-Grade Non-Hodgkin's Lymphoma

In an era of concern about age bias in cancer treatment, many investigators believe that doctors, prejudiced by experience with intolerable toxic effects in the aged, are not offering appropriate treatment to older (≥60 years) patients (1,2). Although it is well known that aging is associated with many pathophysiologic alterations that result in an increased risk of hematopoietic, mucosal, cardiac, and neurologic toxic effects (1-3), the pharmacodynamics of antineoplastic agents in the elderly is virtually unexplored, and definite models of dose adjustment in accordance with age do not exist (3).

Clinical trials of chemotherapy in elderly patients with non-Hodgkin’s lymphoma have yielded conflicting results in terms of both response and toxicity (2,4-6). O’Reilly et al. (6), using low-dose ACOP-B (doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone), reported a 65% complete response rate in 40 elderly patients. There were two treatment-related deaths, and only 15% of the patients had grade 3-4 neutropenia (Eastern Cooperative Oncology Group classification). The investigators concluded that the regimen is an effective one with tolerable toxic effects.

We recognize the need to offer older patients a decent treatment option for a systemic malignancy. Chemotherapy represents the primary and potentially curative form of treatment, and the results with brief-duration (8-12 weeks) intensive chemotherapy regimens have been encouraging (5-8). Thus, we began a prospective phase II trial to study the efficacy and toxicity of a similar intensive 12-week combination chemotherapy regimen in elderly patients with intermediate-grade or high-grade non-Hodgkin’s lymphoma.

Eligible patients were aged 60-80 years with a good performance status (Eastern Cooperative Oncology Group 1-3); newly diagnosed diffuse large-cell, diffuse mixed cell, or diffuse large-cell immunoblastic lymphoma (working formulation) (9); and advanced stage III or IV disease or bulky stage II disease (Ann Arbor classification) (10). The regimen consisted of 250 mg/m² cyclophosphamide and 30 mg/m² epirubicin on weeks 1, 3, 5, 7, 9, and 11; 1.4 mg/m² (maximum, 2 mg/m²) vincristine and 10 mg/m² (maximum, 15 mg/m²) bleomycin on weeks 2, 4, 6, 8, 10, and 12; 50 mg prednisone daily for 4 weeks, followed by 50 mg prednisone every other day for the remaining 8 weeks; and 300 mg allopurinol daily, antibiotic on the first 3 days of each week, and antifungal prophylaxis daily throughout the treatment.

The first patient, a 60-year-old male with stage II B, bulky diffuse large-cell lymphoma and good partial response, developed grade 4 neutropenia on the 4th week of treatment and died of septic shock. After this episode of myelosuppression, granulocyte colony-stimulating factor prophylaxis was included in the protocol. Three more patients, aged 72, 64, and 75 years, with apparently good performance status and stages III B and II A diffuse mixed cell lymphoma and stage II A diffuse large-cell immunoblastic lymphoma, respectively, were enrolled in the study. The first patient achieved complete remission in the 4th week but treatment was discontinued because of grade 4 neutropenic infection in the 5th week, and the response lasted only 2 months. The second patient completed the treatment, with complete response and one episode of grade 4 neutropenia and remained in remission for 4 months. The third patient developed grade 4 neutropenia in the 7th week of treatment and died of septic shock in partial remission.

Having observed two treatment-related deaths and one case of grade 4 toxicity that required cessation of treatment despite aggressive supportive measures, we were discouraged from continuing the treatment regimen unless we could decrease the myelotoxicity by modifying the dose and the schedule. Our experience emphasizes that aging is a distinct process that cannot easily be defined by years and that individual degrees of functional deterioration, rather than age, indicate the outcome of treatment. Therefore the patient should be evaluated individually before he or she is assigned to some form of therapy.

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References

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Bladder Cancer in a 39-Year-Old Female Pharmacist

A 39-year-old pharmacist presented to her physician with the complaint of painless hematuria. Urinalysis revealed many red and white blood cells too numerous to count, but no pathogens were isolated. A repeat urinalysis 9 days later was negative for hematuria. Another episode of hematuria occurred 5 months later, and the patient was referred for an intravenous pyelogram and urologic consultation. The intravenous pyelogram gave normal results, but cystoscopy revealed an exophytic lesion with a small stalk on the bladder wall. The tumor was removed transurethrally, and the pathology review indicated the presence of World Health Organization grade II papillary transitional cell carcinoma of the bladder without evidence of invasion into the bladder wall.

Twelve years before her diagnosis with bladder cancer, this patient had worked full-time for approximately 20 months as a pharmacist in a hospital intravenous preparation area. She and her co-workers routinely prepared cytotoxic agents for cancer chemotherapy. The most common agents in order of frequency of preparation were cyclophosphamide, fluorouracil, methotrexate, doxorubicin, and cisplatin. Each day, the patient was stationed in the drug preparation area for about 7 hours and prepared two to three mixtures of antineoplastic drugs for intravenous use. When preparing solutions, she was required to use a horizontal laminar-flow hood that directed air flow outward into the room and toward her. There were no special precautions to prevent aerosol formation or to contain the exhaust of contaminated air. This patient has had no other unusual exposures to known occupational or environmental carcinogens and has been a life-long non-smoker and a vegetarian for more than 13 years.

The potential hazards of occupational exposure to antineoplastic drugs have been of concern for more than 20 years (1). Numerous studies (2-7) have been conducted to assess exposure of hospital personnel who prepared and administered these drugs. Compared with unexposed hospital workers, pharmacists and nurses who handled antineoplastic agents excreted increased amounts of urinary mutagens (8-10), with mutagenic responses increasing over the work week and resolving with the elimination of exposure. Chromosome studies in these workers also showed increased frequency of lymphocytic sister-chromatid exchange (11-13), as well as other chromosomal abnormalities (13,14). Cyclophosphamide metabolites also have been identified in the urine of nurses who have administered this drug (7). In contrast, hospital pharmacists who had prepared these agents while working under vertical laminar-flow hoods, which draw air up into a cabinet and through a filter away from the worker, did not show increased urinary mutagenicity (9,10,15).

Occupational exposure to antineoplastic agents also is teratogenic. Epidemiologic studies have reported increases in spontaneous abortions and congenital malformations in pregnant nurses and doctors occupationally exposed to these cytotoxic agents (16-19).

Evidence that exposure to alkylating antineoplastic drugs is carcinogenic in humans also derives from data on patients treated with therapeutic doses of these agents, especially cyclophosphamide, for malignant and nonmalignant disorders. Case reports and epidemiologic studies have shown excesses of subsequent secondary malignancies, including bladder cancer (20-24). The latent period for these subsequent malignancies has ranged from 5 to 12 years (23,24). The International Agency for Research on Cancer considers cyclophosphamide to be a human carcinogen (group 1) and cisplatin and doxorubicin to be probable human carcinogens (group 2A) (22,25,26). Guidelines currently exist to minimize exposure of health professionals who mix and administer intravenous cancer chemotherapeutic agents (27-30).

During the past 50 years, bladder cancer risk and occupational exposures have been studied extensively (31-33). New high-risk occupations have been identified, and increased risk has been noted among both men and women (34-36). In epidemiologic studies of occupational exposure that were based on job titles as a proxy for specific exposures, increased risks of bladder cancer have been reported for medical workers, including nurses and pharmacists (37-41). While an association between bladder cancer risk and individuals ever employed as pharmacists has been noted, whether this risk is associated with antineoplastic agents has not been investigated. However, a small, nested case-control study of leukemia and non-Hodgkin’s lymphoma (42) showed that Danish physicians who worked in hospital departments where antineoplastic drugs were administered had nearly a threefold excess risk of leukemia, compared with physicians who worked elsewhere.

Cancer of the bladder is primarily a disease of older White men; approximately two thirds of the cases occur in people who are aged 65 years and older (33). In the San Francisco-Oakland Metropolitan Statistical Area, where our patient resides, the average annual age-specific rate for papillary cancer of the bladder for women aged 35-39 years is only 0.5 per million per year (1981-1988) (San Francisco Bay Area Surveillance, Epidemiology, and End Results [SEER] program of the National Cancer Institute [NCI] data 1981-1988, unpublished). Since our patient had none of the known risk factors for bladder cancer, her risk should have been lower than the rate for all women in her age group.

The importance of obtaining an occupational history from patients with hematuria and aseptic urine is underscored by the following findings: evidence that occupational exposures to antineoplastic drugs are highly mutagenic (8-10) and teratogenic (16-19); evidence that the...