

Body Wars: Effect of Friendly Fire (Cancer Therapy)

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Cancer is a civil war raging within the body. When the malignant forces overwhelm normal tissue, reinforcements are required, including the surgical knife, radiation, and chemicals. These powerful, but sometimes undisciplined, allies often overcome the cancer cells, holding them in check or destroying them completely. In annihilating the rebel strongholds, however, the curative armies occasionally go too far, and "friendly fire" can affect normal cells, causing death, havoc, or life-threatening change. Nearly 40 years ago, the energies of supervoltage x rays and chemotherapy were marshaled to combat Hodgkin's disease, and they heralded the modern era of cancer therapy (Z). Today, cures and long-term survival are possible for 75% of patients. This remarkable victory, however, is not without consequences, because approximately one in nine patients develops a new cancer within 15 years.

Second cancers after Hodgkin's disease have been intensely studied for more than 20 years (2-5). Leukemia develops shortly after chemotherapy but is infrequent among long-term survivors. Cancers of the lung, breast, thyroid, stomach, and bone follow high-dose mantle radiotherapy after a latent period of 5-10 years. Non-Hodgkin's lymphoma and melanoma appear related to immune dysfunction and not directly to treatment. Splenectomy seems to exert an independent effect on risk for leukemia. Radiation dose to specific organs and the amount of administered alkylating agents profoundly influence future risk, as does age at treatment. The potentiating effects of cigarette smoke and host factors as well as the possible interactive effects of systemic chemotherapy with radiation treatment have not been well studied. Because the armamentarium most often includes drug combinations, it has been difficult to determine the carcinogenic potential of individual agents. Only a few studies have attempted to quantify risk in terms of radiation dose or cumulative drug dosage.

To provide additional quantitative data on risk of second cancer, Boivin et al. (6) presented a third follow-up of an expanded study of 9280 1-year survivors of Hodgkin's disease who were treated at one of 14 different clinical centers. Overall, 521 patients (or 5%) developed a new invasive cancer, whereas the expected number would have been 191 (or 1.8%) based on general population rates and an average follow-up of 7.1 years. In absolute terms, an extra five cancers per year occurred per 1000 patients. Leukemia and cancers of the digestive organs and respiratory system accounted for 6270 of the 330 excess cancers. These overall results are generally consistent with prior findings from larger series (7,8). There are a number of important new observations and inconsistencies, however, that will require confirmation and resolution.

As previously reported, potent chemical agents that destroy rapidly proliferating cancer cells were found to damage hematopoietic organs and lead to leukemia. However, several drug associations with leukemia found in the study by Boivin et al. (6) were not anticipated. Vinblastine, a plant alkaloid, was reported to increase leukemia risk twofold, although this agent has not been previously shown to cause cancer in animals or humans. In contrast, mechlorethamine (nitrogen mustard, the "M" in MOPP [i.e., mechlorethamine, vincristine, procarbazine, and prednisone]) and cyclophosphamide are alkylating agents of proven leukemogenicity (9-11), yet no elevated risks were identified within the current series. Procarbazine alone was reported to increase leukemia risk nearly fivefold, which is potentially a new finding, but this observation conflicts with current understanding that procarbazine may have a lower leukemogenic effect than mechlorethamine (3). While the attempt by Boivin et al. (6) to tie specific risks to individual drugs and drug combinations is commendable, there remain lingering doubts as to the degree of success. Concerns are raised by the absence of information on drug dosage (precluding dose-response evaluations), uncertainty as to the completeness of reported salvage therapy given years later for relapse to a significant proportion of patients, and doubts about whether individual drug effects can be clearly distinguished statistically amid a fog of other cytotoxic agents as well as radiation.

To conquer cancer, it remains necessary to unleash the toxic power of chemical and radiation energy within the body. Adverse effects seen today, however, mirror the treatments of yesteryear and are not strictly applicable to current regimens that assault tumors with more lethal force and normal tissue with less toxicity. ABVD (i.e., doxorubicin, bleomycin, vinblastine, and dacarbazine), for example, appears less leukemogenic than MOPP, and linear accelerators provide higher radiation dose to tumors with less collateral tissue damage. Constant vigilance is necessary, however, to monitor the risks of new therapies, such as the use of epipodophyllotoxins (9) and bone marrow transplantation (12).

The extent to which chemical warfare causes auxiliary damage to normal tissue remains an important area for future research. Chemicals can cause very high relative increases in leukemia, a rare disease. If the late effects of drug therapy paralleled those seen after radiation exposures (13), enormous, increases in solid tumors would have been expected. It is thus

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noteworthy that the many years of follow-up in the study by Boivin et al. (6) and other series (7,8) have not revealed a general epidemic of drug-related solid cancers. Nonetheless, focused case-control (or case-cohort) studies with detailed information on drug and radiation dose are needed to quantify the level of solid cancer risk attributable to combined modality therapy. Molecular forensics might also be applied to link specific changes in tumor DNA to specific treatments, such as unique p53 mutations in lung cancers following radiotherapy (De Benedetti VM, Travis LB, Welsh JA, et al.: manuscript submitted for publication) or in bladder cancers following cyclophosphamide administration (14). The role of immune dysfunction, host, and life-style factors should also be further elucidated.

Following a successful treatment, the best offense is now a good defense. Survivors should undergo routine mammographic screening to permit early detection of treatment-related breast cancer and ongoing dermatologic evaluation of dysplastic nevi and other melanoma precursors. They should be advised to apply sunscreen when outdoors, to avoid tanning parlors, and to stop smoking in order to reduce any potentiating effect of tobacco-related carcinogens. In addition, survivors should be encouraged to follow proper nutritional guidelines on the chance that dietary factors might modulate future risk of cancer and also heart disease (15). All patients should be followed for life, but especially survivors of childhood Hodgkin's disease (16,17). However, despite the consequences of friendly fire on normal tissue, the phenomenal success of treatment for Hodgkin's disease is ground gained in the battle against cancer.

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