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Editorial

The carcinogenic potential of cytotoxic chemotherapy and its implications for therapeutic decision-making

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The experimental carcinogenicity of many anticancer agents is now cell established [15, 16]. There is a growing body of data indicating that some of these agents have the ability to induce second tumors in man when used in certain therapeutic situations. The agents implicated to the greatest degree in the human studies are the alkylating agents, nitrosoureas, and procarbazine. The most commonly reported on second malignancy induced appears to be acute non-lymphocytic leukemia. The actual incidence of solid tumors may be greater but is less clearly analyzed. Increased incidences of secondary leukemia have been reported after treatment with L-phenylalanine mustard in ovarian cancer [8, 13] and multiple myeloma [1]. The MOPP regimen (nitrogen mustard, vincristine, procarbazine, and prednisone), and similar type regiments containing alkylating agents and procarbazine, have resulted in increased incidences of leukemia in patients with Hodgkin's disease also exposed to total lymphoid irradiation [4, 5, 7, 11, 17]. Recently, reports of the nitrosourea semustine (methyl-CCNU) causing leukemia in patients with colorectal and gastric cancer on adjuvant chemotherapy protocols have also been reported [2, 3].

In these times of increased scrutiny of cancer treatment research, with particular emphasis on the toxicity of cancer therapy in general and cancer chemotherapy in particular, these reports are causing an increased level of anxiety and agitation in the clinical research establishment. This takes place in a climate of diminished funding for cancer research, a sense of disillusionment with the perceived overpromise of the National Cancer Program, and increased emphasis on prevention research at the expense of treatment research, and a near constant level of congressional and media study of the cancer treatment establishment. In this climate it is easy to lose some perspective on the issue of the carcinogenicity of anticancer agents.

A critical aspect of analyzing the true risk of second tumors induced by cytotoxic agents is the existence of a meaningful data set which includes:

1. a well-defined and adequately sized denominator;
2. adequate follow-up;
3. an appropriate control group; and
4. acceptable statistical methodology.

The analysis must take cognizance that carcinogenicity is a multifactorial process and that patients with one malignancy are at a greater risk of developing a second malignancy than a population that has never developed cancer. In addition, if patients with their first malignancy live longer as a result of therapy, is the development of a second malignancy due to a longer time-frame for a second malignancy to clinically express itself, the therapy itself, or some combination of both?

The ideal study to evaluate the importance of therapy in development of second malignancy is a prospectively randomized study in which the initial neoplastic disease and stage are comparable and the only variable is therapy. Such studies exist with adjuvant chemotherapy. A review of the adjuvant chemotherapy literature utilizing alkylating agents or nitrosoureas shows that in none is there statistically significant increases of second tumors in the treated vs the control group. This includes the adjuvant breast studies utilizing L-phenylalanine mustard by the NSABP [9] and the CMF study of Banadonna [14] which includes cyclophosphamide. If all of the bowel and gastric cancer and adjuvant studies with semustine are studied, as individual studies, none shows a statistically significant increased incidence of secondary leukemia or malignancy. The major weakness in depending exclusively on these studies is that their numbers are very small for the type of epidemiologic analyses of incidence which are used to demonstrate increased risk of malignancy. With studies comparing risk in cohorts of 100–300 patients each, the differences to be significant would have to be quite large.

The analyses that have demonstrated increased risk due to therapy have been of several types. The most common type is the retrospective analysis of a cumulative cohort taken from several studies and the incidence in that cohort compared to the expected incidence in a population, *without prior malignancy*, as derived from large scale tumor registry data bases. From this, a relative ratio of incidence or risk is devised to express the difference. There are several weaknesses in these types of analyses. The first is that the tumor registry data base is a population-based one while the therapy cohort is a highly selected population with pre-existing tumor, selected for and participating in a sophisticated clinical research study and with adequate follow-up within that study. In essence, the control group is a massive, poorly analyzed (in comparison to a clinical research population), poorly matched historical control. Its very massiveness makes it intrinsically impressive and allows for small differences to reach the magical (to physicians) levels of statistical significance. A second weakness is that the control group which should be used does not exist (or hasn't been used) within the tumor registry data bases. That control group is the population of similar age, with the same first malignancy, followed-up for a comparable period of time.

A second type of analysis looks at a cohort of patients treated in several protocols, within a cooperative group or single institution. These patients are divided retrospectively

into certain broad subsets with comparisons being made between the incidence of second malignancies within these subsets and within each subset to the tumor registry historical control. This is what has occurred with combination chemotherapy in Hodgkin's disease [6]. This type of retrospective subsetting has shown that combination chemotherapy with MOPP, or most MOPP-like regimens, either alone or in combination with irradiation, at any time in the patients course, gives an increased risk of secondary acute non-lymphocytic leukemia. This risk is greater than with irradiation alone which does not demonstrate a significantly higher rate than seen in the tumor registry historical control. This type of analysis suffers from all the same weaknesses already discussed in relation to the historical control. Its greater strength lies in the comparisons that can be made within the treated Hodgkin's disease data base itself. This type of analysis, however, must still recognize the interpretative problem of retrospectively and late into analysis, creating new subsets for analysis. These new subsets created may contain within them important imbalances for critically important prognostic variables for the end-point of the analysis. Since these Hodgkin's disease studies were designed as therapy protocols, and not as epidemiologic studies of second tumor risk, this factor should be given some consideration in the interpretation of the data.

Recently Boice et al. [3] have studied leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with methyl-CCNU. The patients they evaluated were treated with adjuvant chemotherapy for large bowel or gastric cancer in nine randomized clinical trials conducted by four cooperative oncology groups. All the patients receiving methyl-CCNU also received 5-fluorouracil and some received other therapies as well such as radiotherapy and/or immunotherapy. The period of observation for calculating the risk of developing acute leukemia ranged from 1974 to 1980 and was calculated from the data of initial therapy. The data were compared to the historical control of the 5-year age, sex, and calendar year incidence rates of acute non-lymphocytic leukemia (ANL) from the Connecticut tumor registry. Therefore a relative risk ratio was developed against the general population of Connecticut.

A total of 3,633 patients were enrolled in the nine clinical trials and they accrued 10,779 person years of observation. A total of 2,067 patients received methyl-CCNU. In the group there were seven cases of ANL and seven cases of either preleukemia or acute myelodysplastic syndrome, in 6,146 person years of observation. In the general population of Connecticut, the expected incidence of ANL, in this number of patients would be 0.71 so that the relative risk is 9.9 with the confidence interval raising from 3.9 to 20.0. After 5 years of observation, the cumulative probability of developing a leukemia in the population rose to 2.1% ± 0.8%. The overall incidence of leukemia complications among patients receiving methyl-CCNU was 2.3 cases per year per 1,000 persons.

The most persuasive evidence of the risk from methyl-CCNU comes from analyzing the 1,566 persons in those nine protocols who did not receive methyl-CCNU. In this group only one case of ANL was observed in 4,633 person years of observation. The relative risk from this group was not greater that that for the general population of Connecticut. This internalized concomitant (but non-randomized) control lends increase credibility to the use of the broader historical control. It is worth mentioning that in none of the nine randomized studies themselves was there a significant difference in the ANL incidence between those treated with methyl-CCNU and those not. In addition, the incidence of ANL after methyl-CCNU differed greatly in different trials for reasons, Boice et al. state, they cannot explain.

How should the data on second tumors after cytotoxic therapy be interpreted in relation to clinical practice recommendations and to the design of clinical research? All cancer therapy must be analyzed in terms of cost vs benefit. It left untreated all malignancy is fatal. The benefit of cure, (long-term disease-free survival) must be balanced out against the cost of surgical mortality and morbidity, and the risk of acute and chronic toxicities from irradiation and cytotoxic therapy. An incidence of secondary leukemia of 2–5% at 10 years should be placed into the context of an immediate operative mortality of 2–5% for some of the major curative intent radical surgical procedures. The only relevant issue is: does the benefit outweigh the risk? It is interesting to note that other investigations by Congress and the lay press do not focus on surgical operations such as the Whipple procedure and radical esophageal cancer surgery, in which cure is an uncommon event and surgical morbidity and mortality quite high. For some undetermined psychosocial reason, cytotoxic chemotherapy gets the lions share of emphasis on side effects independent of benefit.

Each situation in which chemotherapy is implicated as causing secondary malignancy must be examined objectively in terms of therapeutic ratio. If the benefit is cancelled out by the risk then the therapy should not be recommended to the oncologic community. If the benefits do outweigh the risk then both aspects should be clearly understood and clinical research should pursue objectives of diminishing risk along with improving benefit. This is, in fact, what is happening in Hodgkin's disease where chemotherapy regimens are now being tested in combined modality settings which have been designed specifically to exclude known carcinogenic agents.

It would be a serious mistake to draw regulatory generalizations about the carcinogenicity of cancer drugs from the specific research experience available so far. Each clinical research therapeutic situation should be analyzed separately. The carcinogenicity of cancer drugs should not be viewed separately or differently than the mortality risk from surgery and irradiation, and within the context of the mortality risk from withholding the therapy in question.

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