Second Tumors in Treated Cancer Patients: Implications for Life Underwriting

Hank George, CLU, FALU
Manager of Medical Services
Northwestern Mutual Life Insurance Co.

Medical directors and their underwriter colleagues are routinely asked to assess the insurability of treated cancer patients. These applicants are often enjoying protracted disease-free remissions following aggressive multimodal therapy.

The increasing number of insurance buyers who have been treated with chemotherapy and/or radiotherapy is a result of three developments in clinical medicine. First, the effectiveness of aggressive therapies has led to a steady rise in the percentage of long-term survivors with certain tumors. Hodgkin's disease, testicular cancer and childhood acute lymphocytic leukemia are notable examples. Second, adjuvant chemotherapy is now being given to stage I and early stage II cancer patients who were previously managed with surgery and radiation only. Finally, cytotoxic drugs are also administered in stubborn cases of various non-neoplastic diseases. At least one such disease, psoriasis, has little extra mortality risk. A number of the others are apt to be insurable after achieving a sustained remission (e.g., Crohn's disease, rheumatoid arthritis).

Both chemotherapy and radiotherapy produce immediate and delayed side effects. Because insurance is almost invariably postponed during treatment, it is the delayed complications which are most significant from an underwriting point of view. These late effects may be deferred for years, even decades. When they do surface, the original disease is often in complete remission and the patient may be described as cured. Because of dramatic improvements in apparent cure rates of Hodgkin's disease and certain other cancers, many insurers will now issue policies within a few years of diagnosis and treatment. Coverage may be offered with modest temporary extra premiums payable for five years or less; thereafter, survivors usually pay the standard premium rate. Furthermore, insurance is being granted to some applicants who had advanced malignancies, particularly Hodgkin's disease.

In terms of its implications for insurability, the most important late effect of chemotherapy and radiotherapy is a treatment-provoked second malignant tumor. Overall, the most prevalent second tumors appear to be of lymphoid (non-Hodgkin's lymphomas) and myeloid (acute myelogenous leukemia) origin. This paper explores three questions concerning these second cancers:

1. What is their incidence?
2. What are their possible etiologies?
3. What factors are associated with an increased risk of developing a second tumor?

The Incidence Of Second Tumors In Hodgkin's Disease Survivors

To develop data on the incidence of second malignancies in treated cancer patients, we must look to Hodgkin's disease survivors for most of our data. Second cancers are associated with radiation and drug therapies and these modalities account for an enlarging population of long-term survivors in Hodgkin's disease.

In a 1979 lecture to the American Society of Clinical Oncology, Vincent T. DeVita reported on a series of advanced Hodgkin's patients treated with the MOPP* regimen. Sixty-eight percent (68%) of patients who obtained a complete remission were continuously relapse-free five years after stopping all therapy. Fifteen of these patients died of unrelated causes. At autopsy, fourteen had no evidence of Hodgkin's disease (the fifteenth had an equivocal area in the retroperitoneum that could not be positively diagnosed as residual disease). DeVita's findings and those of other investigators demonstrate that a large percentage of Hodgkin's patients are being cured as a result of aggressive therapy, thus providing a suitable population to study for evidence of second cancers.

A number of reports in the recent literature identify a disturbing incidence of new tumors in

*M.O.P.P. consists of Mustargen (Nitrogen Mustard), Oncovin (Vincristine), Procarbazine and Prednisone.
Hodgkin’s survivors. Nelson and her colleagues found eleven second cancers in 248 patients treated between 1960 and 1977. The median interval between the Hodgkin’s diagnosis and the discovery of the new cancer was approximately ten years. Among those patients treated solely with radiation, the ratio of observed to expected new tumors was slightly greater than 16:1. This increased to more than 26:1 in patients who received both radiotherapy and chemotherapy.\(^2\)

A report in the British Medical Journal (1980) revealed an overall incidence of second tumors in 764 Hodgkin’s survivors of 7.3% after ten years. The incidence of acute leukemia among those patients treated with both radiation and MOPP was 5.4% in just five years.\(^3\)

A summary report from the National Cancer Institute provides a detailed assessment of second tumors according to the type(s) of therapy:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total</th>
<th>Observed/Expected Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Intensive Therapy</td>
<td>131</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>Radiation Only</td>
<td>149</td>
<td>3.8 : 1</td>
</tr>
<tr>
<td>MOPP Only</td>
<td>110</td>
<td>3.2 : 1</td>
</tr>
<tr>
<td>MOPP/Relapse/Radiation</td>
<td>31</td>
<td>6.3 : 1</td>
</tr>
<tr>
<td>Radiation/Relapse/MOPP</td>
<td>34</td>
<td>1.8 : 1</td>
</tr>
</tbody>
</table>


Nearly all the second tumors in patients treated with both radiation and MOPP were acute non-lymphocytic leukemias, leading to the conclusion that “the risk of developing AML in patients who received both MOPP and radiotherapy...may be expected to approximate 5% at ten years.”\(^4\)

Another report of 613 Hodgkin’s survivors disclosed twelve second tumors, of which seven were acute leukemias. In this series, there were no second cancers among patients who received only radiation. Nine of the twelve tumors occurred in patients who received both chemotherapy and radiation.\(^5\) Grunwald and Rosner reviewed 216 Hodgkin’s disease cases which culminated in non-lymphocytic leukemia. Only 10% arose in patients who received radiation alone. By contrast, 62% developed where both radiation and chemotherapy were administered and 15% emerged in patients treated only with cytotoxic drugs.\(^6\)

The actuarial risk of developing acute leukemia following multimodal therapy for Hodgkin’s disease has been calculated as 3.9% over the first seven years after cessation of treatment. This assessment was based on 680 Hodgkin’s cases and seven subsequent leukemias.\(^7\) A series of patients from the Denmark Medical Institute (391 cases of Hodgkin’s; seventeen later leukemias) showed the cumulative probability of leukemia to be 3.9% at five years and 9.9% at nine years. All seventeen patients who developed leukemia received chemotherapy or multimodal therapy. There were no cases of leukemia in 79 patients treated solely with radiation.\(^8\)

Although leukemia is the predominant second cancer in Hodgkin’s survivors, a wide variety of other tumors have also been seen. The most prevalent is non-Hodgkin’s lymphoma (NHL). A report by Krikorian in the New England Journal reviewed six cases of NHL in treated Hodgkin’s patients. The latency period ranged from 44 to 124 months and the actuarial risk of developing NHL within ten years of multimodal therapy was 15.2%.\(^9\) A more recent assessment in the Archives of Internal Medicine reviewed 29 cases of non-Hodgkin’s lymphoma arising after Hodgkin’s. Four patients were treated with radiation only and eighteen had a combination of chemotherapy and radiation. The median latency period from Hodgkin’s diagnosis to the onset of NHL was 48 months (range: 12-156 months).\(^10\)

In addition to non-Hodgkin’s lymphoma, other invasive malignancies in Hodgkin’s survivors include carcinomas of the lung, skin, breast, colon, thyroid gland, bladder, kidney and testicle as well as osteogenic sarcoma and plasmacytoma.\(^11\) In many of these cases, there is strong evidence suggesting the second tumors were related to therapy.
Potential Causes Of Acute Leukemias And Other Second Tumors In Treated Hodgkin's Patients

Are these second tumors a reflection of the natural history of Hodgkin's disease? Are Hodgkin's patients inherently at increased risk for later myeloid and lymphoid neoplasms and is it the lengthy survival of successfully-treated patients which allows this potential to be realized in some cases?

Careful assessment of immune function before and after treatment has shown that Hodgkin's disease is associated with abnormal cell-mediated immunity. Researchers have found reduced quantities of T-lymphocytes and diminished in vitro T-cell activity. This can be seen in the absence of therapy and may even antedate the onset of the Hodgkin's disease. T-cell immunity is primarily responsible for cancer surveillance.

There is evidence of a possible direct association between Hodgkin's disease and the development of subsequent hematological and lymphoreticular cancers. Recent reports document both Sezary Syndrome (cutaneous T-cell lymphoma) and Burkitt's leukemia (B-cell immunoblastic leukemia) occurring simultaneously with Hodgkin's or arising after therapy. Other investigators have found later acute myelogenous leukemia in patients with chronic lymphocytic leukemia, even in the absence of therapy. Is there a possible etiological relationship between some lymphoid and myeloid neoplasms, perhaps related to a common hematopoietic stem cell? Such a relationship might account for the frequent cases of acute non-lymphocytic leukemia in Hodgkin's patients. If there is an association between lymphoid and myeloid cancers, one would expect an increased incidence of leukemia in patients with non-Hodgkin's lymphomas. The evidence is controversial:

A Manitoba study revealed thirty-four second cancers in a population of 630 non-Hodgkin's lymphoma (NHL) patients followed as long as a decade. Sixty-seven percent (67%) had chemotherapy with one or more drugs, yet there were no leukemias among the second tumors.

Several reports contradict the Manitoba findings. In one, five cases of acute myeloproliferative neoplasia were discovered following NHL therapy. Four patients had extensive irradiation and chemotherapy. Zarrabi reviewed sixty-five cases of NHL associated with subsequent acute non-lymphocytic leukemia. All major varieties of NHL were represented. Ten patients had radiation only and thirteen received solely cytotoxic drugs; the remainder had both modalities. There were also solid tumors reported but their incidence approximated the expected number in a general population. The conclusion was that the only excessive second cancer in NHL patients is acute non-lymphocytic leukemia.

The foregoing reports document an increased incidence of myeloid leukemias in patients with lymphoid cancers. If these leukemias are not an expression of the natural history of such tumors, then perhaps the leukemogenic effects of one or more forms of therapy are responsible. A review of the evidence for this possibility helps put this question in perspective:

Radiation and certain classes of cytotoxic drugs are known to induce cancer. Among the drugs, it is the alkylating agents along with procarbazine and the nitrosoureas which give evidence of a definite carcinogenic effect. The alkylating agents include nitrogen mustard (Mustargen), chlorambucil (Leukeran), melphalan (Alkeran, L-PAM), cyclophosphamide (Cytoxan) and busulfan.

Chemotherapeutic drugs may contribute to the induction of cancers by several mechanisms. First, they cause mutagenic chromosomal changes. They damage the bone marrow, resulting in chronic cytopenias and potentiating marrow damage wrought by radiation. Finally, they are immunosuppressive and may promote oncoviruses that would otherwise be eliminated by the host's immune system.

The incidence of cancer in immune-compromised individuals is dramatic. As of 1979, there were 733 de novo malignancies in organ allograft recipients. One hundred-fifty (150) were lymphomas. Many other studies testify to the relationship between immunosuppression (naturally-occurring or induced by therapy) and the risk of malignancy. And a disproportionate share of these malignancies are of lymphoid origin.

In 1978, Parmley and associates reported on the ultrastructural and immunocytochemical analysis of a patient who developed acute myelomonocytic leukemia after treatment of Hodgkin's disease. Their findings were consistent with the hypothesis that this leukemia was a second primary cancer of iatrogenic origin, supporting the argument that such tumors are induced or at least promoted by chemotherapy and radiotherapy.

The alkylating agent busulfan was shown to induce dysplasia in humans as early as 1965. Several reviews of myeloma patients treated with melphalan or one of the nitrosoureas have shown an increased incidence of later myeloid leukemias. Melphalan has also been used extensively in managing advanced ovarian carcinoma. Reimer reported on twelve acute non-lymphocytic leukemias among ovarian cancer patients who received alkylating agents. This
was calculated to be 171.4 times the expected incidence, leading the author to conclude "...leukemia would be expected to develop in 5-10% of a group of (these) patients surviving for ten years." This and other reports confirm the strong relationship between melphalan and later leukemia.22

Further evidence for the leukemogenicity of the nitrosoureas is offered by a report of two patients given BCNU, CCNU and/or Methyl CCNU for brain tumors who developed acute non-lymphocytic leukemias more than four years after therapy.23 Two patients who received BCNU along with an alkylating agent and procarbazine for lung cancer also developed subsequent acute non-lymphocytic leukemia.24

Chlorambucil and cyclophosphamide are linked to acute leukemias following intensive or long-term therapies. The case against chlorambucil is established through reviewing breast cancer patients given this alkylating agent as a post-mastectomy adjuvant. Learner reported on three cases of acute myelogenous leukemia four to six years after low-dose chlorambucil.25 Rosner, Carey and Zarrabi summarized 78 cases of acute myelogenous leukemia following breast cancer. The majority received just radiation following mastectomy. Seven had surgery alone and eight had chemotherapy. The overall incidence of acute leukemia was estimated to exceed seven times the anticipated rate. Because of the leukemias in patients treated only surgically, the etiologies of these leukemias must involve more than just delayed drug and radiation toxicity.26

A recent report showed acute myelomonocytic leukemia arising sixteen months after chemotherapy (including cyclophosphamide) and radiation for Ewing's Sarcoma. Cyclophosphamide was also associated with acute leukemia following treatment of oat-cell lung cancer.27

Alkylating agents are also used to treat severe cases of certain non-neoplastic diseases. In 1979, Grunwald and Rosner summarized fifty-eight cases of acute leukemia following cytotoxic drug therapy for non-malignant diseases. Thirty patients received only alkylating drugs. An additional eighteen had multiple agent therapy including alkylating drugs. Among the diseases were rheumatoid arthritis, chronic active hepatitis, multiple sclerosis, lupus erythematosus and psoriasis.28

Although this paper is concerned primarily with incidence of second tumors in cancer patients, insurance applicants who receive alkylating agents for non-neoplastic diseases also present special underwriting problems. If their treatment included intensive and/or long-term drug therapy, there is a definite risk of later leukemia. The degree of that risk is still largely a matter of conjecture.

Characteristics Of Therapy-Included Leukemias

Acute myeloid leukemias in patients treated with anti-cancer drugs and/or radiation have distinctive features. Virtually all have been acute and non-lymphocytic. The most prevalent varieties are myelocytic, monocytic and myelomonocytic leukemia and erythroleukemia. Chronic leukemia does not appear as a consequence of therapy. Lymphocytic leukemias are rare, although several cases of Burkitt's (immunoblastic) leukemia have been described (see above).

Careful evaluation of patients with treatment-provoked leukemia has disclosed many cases preceded by a preleukemic phase. This phase is heralded by chronic cytopenias involving the red blood cells, granulocytes and/or platelets. Rowley and associates found a definite preleukemic stage in twenty of twenty-six patients who developed overt leukemia.29 Other researchers have discovered an equally high frequency of preleukemia culminating in rapidly-fatal leukemias.30

The preleukemic phase typically presents as a pancytopenia. Among the features in the peripheral blood are leukopenia/neutropenia, refractory anemia, thrombocytopenia (or thrombocytosis), macrocytosis, nucleated red cells, basophilia, monocytosis, immature granulocytes and a marked degree of morphological variability among red blood cells (anisopoikilocytosis). In addition, a sideroblastic anemia is common.

These finding have been reported by numerous observers.31 Reviewing 190 cases of acute non-lymphocytic leukemia following treatment for Hodgkin's disease, Cadman and his co-workers noted that the cytopenic findings typically included low levels of hemoglobin (10.5 or less), hematocrit (32% or less), white blood cells (less than 4,000 cu/mm) platelets (less than 150,000 cu/mm). The presence of individual cytopenias is more significant if the overall profile is pancytopenic.32

The duration of the preleukemic phase has ranged from a few months to twenty months or longer.33 Among the 216 patients reported by Grunwald and Rosner, seventy-three had a discernible preleukemic stage. The median duration was just over eight months.34

Survival after the diagnosis of therapy-related leukemia is short. Only a few patients have lived more than one year. Most do not respond to therapy. One of the most important factors in therapy-related leukemias is the latency period from the diagnosis of the original tumor to the emergence of leukemia. Table 2 identifies the latency periods reported in six series. While some patients developed leukemia within a year...
of the onset of Hodgkin's disease or non-Hodgkin's lymphoma, there were many leukemias deferred for a decade or longer: others treated with these therapies may not be legitimate standard risks as early as six or eight years after completing treatment. The second

### TABLE II

Reported Latency Periods in Therapy-Related Leukemia

<table>
<thead>
<tr>
<th>Source (Year)</th>
<th>First Tumor</th>
<th>Latency Periods to Leukemia Onset (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson (1981)</td>
<td>Various</td>
<td>Mean/Median 53.0 (Median)</td>
</tr>
<tr>
<td>Baccarani (1980)</td>
<td>Hodgkin's disease</td>
<td>Mean/Median 42.0 (Median)</td>
</tr>
<tr>
<td>Cadman (1977)</td>
<td>Hodgkin's disease</td>
<td>Mean 67.8 (Mean)</td>
</tr>
<tr>
<td>Grunwald and Rosner (1982)</td>
<td>Hodgkin's disease</td>
<td>Mean 73.4 (Mean)</td>
</tr>
<tr>
<td>Kapadia (1980)</td>
<td>Various</td>
<td>Mean 60.0 (Mean)</td>
</tr>
<tr>
<td>Zarrabi (1980)</td>
<td>Non-Hodgkin's lymphoma</td>
<td>Mean 63.0 (Mean)</td>
</tr>
</tbody>
</table>

### Implications For Life Underwriting

It is now clear that patients who receive certain chemotherapeutic drugs and/or extensive radiation have a definite, long-term risk of developing second cancers, particularly acute non-lymphocytic leukemia. This risk is greatest if chemotherapy includes one or more alkylating agents, procarbazine and/or nitrosoureas. Furthermore, when radiotherapy is also given to patients who received drug treatments, the risk of such tumors increases.

Cancer researchers are aware of this insidious complication and are working to develop new drugs and/or regimens which minimize the risk. For example, the ABVD protocol for Hodgkin's disease contains no alkylating agents or procarbazine and has not been associated with leukemia (although the number of patients and the duration of their follow-up has been relatively short). All of this leaves us with the conclusion that we will continue to see insurance applicants who have been treated with these chemotherapy drugs and/or intensive radiation for years to come.

The foregoing conclusions compel us to consider several questions when evaluating applicants at risk for therapy-related leukemia and other second tumors. First, is a temporary extra premium adequate in these cases? Many researchers believe these patients have an increased lifelong risk of developing second tumors, particularly leukemia\(^\text{35}\). It is, as yet, impossible to say unequivocally if this risk is great enough to justify a permanent adjustment in insurance pricing, but the evidence points strongly in that direction.

In consideration of the protracted latency periods identified above, Hodgkin's patients and consideration is the feasibility of additional requirements to attempt to identify cases with persistent hematological disturbances and/or preleukemia. A blood count may be a cost-feasible approach, particularly in applicants who have not been closely followed by their physicians. Such a profile might include hemoglobin, hematocrit, a white count plus a differential, a platelet count and a smear (to examine cell morphology). Similarly, a careful examination may detect palpable lymph nodes, hepatosplenomegaly, purpura (due to thrombocytopenia), etc. The percentage of cancer patients treated with chemotherapy and/or intensive radiotherapy who are enjoying extended disease-free remissions is increasing. This is particularly true in Hodgkin's disease, acute lymphocytic leukemia of childhood, testicular cancer and certain varieties of non-Hodgkin's lymphoma. A better understanding of the potentials for second tumors in these patients should improve our ability to select insurance risks.

### REFERENCES


