



## The incidence of secondary leukemias

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### ABSTRACT

**Background and Objectives.** The term secondary leukemia is usually employed to indicate both forms of acute myeloid leukemia (AML) evolving from previous myelodysplasia and forms of acute leukemia developing after exposure to environmental or therapeutic toxins or radiation (therapy-related). Secondary leukemias account for 10-30% of all AML. The majority of secondary leukemias resulting from the use of cytotoxic drugs can be divided into two well defined groups depending on whether the patient has received 1) alkylating agents or 2) drugs binding to the enzyme DNA-topoisomerase II. Alkylating agents related leukemias are very similar to post MDS leukemias being characterized frequently by a preleukemic phase, trilineage dysplasia, frequent cytogenetic abnormalities involving chromosomes 5 and 7 and a poor prognosis. Secondary leukemias related to therapy with topoisomerase II inhibitors are not preceded by a preleukemic phase and show frequently balanced translocations involving chromosome 11q23. Among therapy-related leukemias, AML is generally a second neoplasm, thus a predisposition to malignancy, independently from previous chemotherapy, cannot be excluded. This review article examines the incidence of all secondary AMLs and the risk of therapy-related leukemia in relation to the different primary malignancies and treatments.

**Information Sources.** The authors have been working in this field, both experimentally and at clinical level, contributing original papers for many years. In addition, the material examined in this review includes articles published in journals covered by MedLine, reviews in journals with high impact factor and recent reports presented at the *Secondary Leukemia. An Update Symposium* held in Rome in November 1998.

**State of Art and Perspectives.** The incidence of secondary leukemias is increasing because of aging of the population (MDS is more frequent in elderly people) and widespread and successful use of chemoradiotherapy in cancer patients. In the GIMEMA archive of adult acute leukemia (2,964 AML pts from June 1992 to June 1996) an antecedent hemato-

logic disorder (AHD) and/or MDS was found in 8% of all patients (10% of 2,118 patients aged more than 45 years and in 4% of 848 patients aged less than 45). In this series of patients, 6% of all myeloid leukemias were therapy-related leukemia. Therapy-related leukemias are a major problem in patients treated for Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, polycythemia, breast cancer, ovarian carcinoma, or testicular carcinoma. In the GIMEMA archive more than 50% of patients with secondary AML have breast cancer, NHL, or HD. Alkylating agents, nitrosureas and procarbazine appear to have the highest leukemogenic potential. Furthermore aggressive chemotherapy and radiotherapy followed or not by hematopoietic stem cell infusion will produce a more and more prolonged survival but also a greater incidence of secondary AML. Assessment of the risk of secondary leukemia should become part of any therapeutic plan for cancer patients. Avoidance of drugs with more leukemogenic potential will produce a marked reduction of secondary AML.

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Key words: therapy-related leukemia, myelodysplastic syndromes, secondary leukemias

Secondary acute myeloid leukemia (s-AML) can occur following exposure to cytotoxic agents (i.e. drugs, radiation, chemicals) or as a subsequent event in another hematologic disorder, usually myelodysplasia (MDS). Thus the term secondary AML encompasses fundamentally post-myelodysplastic AML and therapy-related AML (t-AML).

### Acute myeloid leukemia following myelodysplastic syndrome

The incidence of secondary leukemias increases with age (Table 1). In the MRC 10<sup>th</sup> AML trial, 135 (7%) of 1,722 patients aged 0-55 years, submitted to intensive chemotherapy for AML had a secondary form.<sup>1</sup> Among 1175 patients aged more than 55 or 60 years submitted to aggressive chemotherapy in four recent multicenter trials<sup>2-5</sup> 286 (24%) were affected by s-AML including post-MDS leukemia and therapy-related leukemias. In the AML GIMEMA (*Gruppo Italiano Malattie Ematologiche dell'Adulto*) archive (2,964 patients from June 1992 to June

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**Table 1. Percentage of patients with *de novo* or secondary AML (s-AML) eligible for intensive chemotherapy trials.**

| Authors, Group   | N. pts. | Age (yrs.) | s-AML N. (%) | De novo CR% | s-AML CR% |
|--|---------|------------|--------------|-------------|-----------|
| Hann <i>et al.</i> , 1997 <sup>1</sup><br>MRC              | 1,722   | 0-56       | 135 (7)      | 83          | 67        |
| Archimbaud <i>et al.</i> , 1997 <sup>2</sup>               | 158     | >60        | 42 (26)      | 65          | 50        |
| Lowenberg <i>et al.</i> , 1997 <sup>3</sup><br>EORTC       | 318     | >60        | 70 (22)      | 56          | 55        |
| Lowenberg <i>et al.</i> , 1998 <sup>4</sup><br>Hovon Group | 489     | >60        | 124 (25)     | 44          | 37        |
| Godwin <i>et al.</i> , 1998 <sup>5</sup><br>SWOG           | 211     | >55        | 50 (24)      | 52          | 24        |
| GIMEMA 1998<br>(unpublished data)                          | 175     | >60        | 14 (8)       | 50          | 40        |

**Table 2. Secondary AML: percentage of post-MDS AML and therapy-related AML (t-AML).**

| References                                | Age (yrs) | Post-MDS AML N. (%) | t-AMLN (%) | Total (%) |
|---|-----------|---------------------|------------|-----------|
| Ruutu <i>et al.</i> , 1994 <sup>6</sup>   | >65       | 11 (84)             | 2 (16)     | 13 (25)   |
| Leoni <i>et al.</i> , 1997 <sup>7</sup>   | >60       | 20 (67)             | 9 (33)     | 29 (44)   |
| Jackson <i>et al.</i> , 1997 <sup>8</sup> | >60       | 9 (75)              | 3 (25)     | 12 (42)   |
| Damiani <i>et al.</i> , 1998 <sup>9</sup> | 25-72     | 38 (70)             | 16 (30)    | 54        |
| GIMEMA*                                   | <45       | 15 (60)             | 10 (40)    | 25 (2.8)  |
| GIMEMA*                                   | >45       | 150 (69)            | 66 (31)    | 216 (10)  |

\*Unpublished data.

1996) an antecedent hematologic disorder (AHD) and/or MDS was found in 8% of all patients (10% of 2118 patients aged more than 45 years and in 4% of 848 patients aged less than 45). Secondary leukemias following MDS accounting for 60-70% of all secondary leukemias (Table 2).<sup>6-9</sup>

Myelodysplastic syndromes can arise *de novo* or be related to exposure to ionizing radiation or myelotoxic drugs.<sup>10-13</sup> The crude incidence of *de novo* MDS is about 3 new cases per 100,000 persons per year, although some authors have reported a higher incidence.<sup>10,11</sup> The age specific incidence rate increases steeply and constantly with age.<sup>11</sup> This increase is markedly higher in females than in males, and is likely to be due to the higher proportion of females in the elderly population.<sup>12</sup> Some authors, such as Aul *et al.*,<sup>11</sup> have reported an increasing incidence of MDS in recent years. This increase probably reflects the

better diagnostic criteria employed and the aging of the population. The incidence of MDS increases with age more than the incidence of leukemia does. According to the data of the co-operative study group reported by Mufty *et al.*<sup>12</sup> about 30% of patients with primary MDS developed AML, the progression into overt leukemia being very frequent in RAEB-t (60%) and in RAEB (44%) and rare in RA (12%) and RAS (8%).

The incidence of therapy-related MDS (t-MDS) in large series of treated patients has not been defined. In the M.D. Anderson hospital series before 1991, t-MDS represented 27% of all MDS,<sup>13</sup> and were probably more common than overt t-AML, considering that macrocytosis and cytopenias, the hallmarks of MDS, can be overlooked in patients with a previous neoplasm. Cytogenetic abnormalities are similar in both *de novo* and t-MDS, but they are more frequent in t-MDS. Deletion or loss of chromosomes 5 and 7 is commonly associated with exposure to alkylating agents. A greater percentage of patients with t-MDS have a high value of the International Prognostic Score.<sup>13</sup> Consequently t-MDS are associated with a poorer prognosis: more than 50% of t-MDS will evolve into AML, but independently of progression to AML, patients with t-MDS have a poorer prognosis than patients with *de novo* MDS.<sup>13,14</sup>

### Therapy-related acute myeloid leukemia

The risk of developing a second malignancy has been estimated to range from 8% to 12% by 20 years after the diagnosis of a first cancer.<sup>15-17</sup> Leukemia is the most frequent secondary neoplasm.<sup>18</sup> Some authors suggest that acute leukemia occurring without chemo-radiotherapy having been administered in the first cancer should not be considered as a secondary leukemia.<sup>18</sup> Yet a second malignant neoplasm is more frequent than might be expected from general population rates, particularly after a first cancer in childhood.<sup>16</sup> Thus, a secondary leukemia following chemo-radiotherapy for a primary neoplasm is mostly related to chemo-radiotherapy performed but probably also reflects an increased susceptibility to cancer.<sup>16,17</sup>

Epidemiologic studies reported increased risks of leukemia after treatment with chemotherapy including alkylating agents such as busulphan, chlorambucil, CCNU, cyclophosphamide, or topoisomerase II inhibitors, such as epipodophyllotoxins or anthracyclines, and after radiotherapy.<sup>18-20</sup>

It is noteworthy that the proportion of secondary acute leukemia is increasing; this is related to widespread use of chemo-radiotherapy, increased survival of treated patients with cancer and aging of the population. Yet different features are present in secondary leukemia induced by DNA topoisomerase II inhibitors and in leukemia induced by alkylating agents and radiotherapy.<sup>18,21-23</sup>

The latency between the previous cancer treatment

and t-leukemia development is longer after alkylating agents (3 to 8 years) and shorter after topoisomerase II inhibitors (2 to 3 years). Leukemia induced by alkylating agents is generally preceded by a myelodysplastic phase, while leukemia induced by topoisomerase II inhibitors is rarely preceded by myelodysplasia. Furthermore in leukemia induced by alkylating agents, it is very frequent to find a complete or partial deletion of chromosome 5 and/or 7.<sup>24</sup> On the other hand, a close association has been found between therapy with topoisomerase II inhibitors and subsequent development of acute myeloid leukemia with abnormalities of 11q23 locus in the context of balanced translocations such as t(9;11), t(19;11) or t(4;11).<sup>21,22</sup>

Therapy-related AML (t-AML) constitutes approximately 5-10% of all AML;<sup>18,25</sup> it has been frequently described to occur after Hodgkin's disease (HD),<sup>19,26-40</sup> non-Hodgkin's Lymphoma (NHL),<sup>41-48</sup> acute lymphoblastic leukemia (ALL),<sup>49-55</sup> multiple myeloma,<sup>56-58</sup> myeloproliferative diseases,<sup>59-63</sup> breast cancer,<sup>20,64-72</sup> ovarian cancer,<sup>73-76</sup> and testicular cancer.<sup>77-79</sup> The risk of developing a t-AML varies in relation to different previous malignancies and previous therapies.

### Hodgkin's disease

Patients with HD constitute the most extensively studied cohort of patients at risk. Several studies convincingly demonstrated that alkylating agents in the chemotherapy schedules are the most important components in determining acute leukemia and MDS. Compared to the general population, the risk of s-AML in HD treated patients has been reported to be 10 to 80-fold greater than in the general population. Overall the 10-year cumulative incidence rate varied considerably ranging from less than 0.3% to 10% (Table 3)<sup>18,19,26-40</sup> depending upon the size of the population studied, the duration of follow up, and the type of therapy administered. The risk of leukemia starts to increase two years after stopping therapy, appears to be maximum in the 5- to 9-year follow-up period, and then drops to near zero after the tenth year of follow-up.<sup>27</sup>

This trend is peculiar to leukemia, most of the other secondary neoplasms only being observed at least 15 years after the diagnosis of Hodgkin's disease.<sup>28</sup> Higher incidence rates have been found in small series of patients treated with regimens such as MOPP (mechlorethamine, oncovin, procarbazine, prednisone) or others, including mechlorethamine and procarbazine or in patients treated with salvage chemotherapy including lomustine.<sup>29</sup>

In MOPP based regimens, substitution of mechlorethamine by cyclophosphamide (COPP) induces a significant reduction of the relative risk of leukemia.<sup>30</sup>

The risk of leukemia is very low or absent in patients treated with radiotherapy only.<sup>31</sup>

Regimens including intercalating topoisomerase II inhibitors, but not including an alkylating agent, such as ABVD (adriamycin, bleomycin, vinblastine, dacar-

**Table 3. Risk of MDS/AML in patients receiving chemoradiotherapy for Hodgkin's disease.**

| References                                     | N. pts. | Therapy | Cases of MDS/AML | CR (%)        |
|--|---------|---------|------------------|---------------|
| Henry-Amar <i>et al.</i> , 1993 <sup>31</sup>  | 5,492   | RT      | 13               | 0.4 (15 yrs)  |
| Blayney <i>et al.</i> , 1987 <sup>27</sup>     | 192     | MOPP    | 12               | 10 (10 yrs)   |
| Andrieu <i>et al.</i> , 1990 <sup>36</sup>     | 462     | MOPP+RT | 10               | 3.5 (15 yrs)  |
| Lavey <i>et al.</i> , 1990 <sup>44</sup>       | 78      | MOPP    | 12               | 2 (10 yrs)    |
|  | 160     | MOPP+RT |                  | 0.9 (10 yrs)  |
| Van Leuwen <i>et al.</i> , 1994 <sup>38</sup>  | 1,939   | CT+RT   | 44               | 4 (10 yrs)    |
| Schellong <i>et al.</i> , 1997 <sup>30</sup>   | 667     | COPP    | 5                | 0.7           |
|  |         | COMP    |                  |               |
|  |         | OPPA    |                  |               |
| Brusamolino <i>et al.</i> , 1998 <sup>39</sup> | 348     | RT      | 2                | 0.3 (15 yrs)  |
|  | 124     | MOPP    | 3                | 2.2           |
|  | 277     | MOPP+RT | 18               | 10.2 (15 yrs) |
|  | 24      | ABVD    | 0                | 0             |
|  | 129     | ABVD+RT | 1                | 0.3           |
| Loefler <i>et al.</i> , 1998 <sup>35</sup>     | 752     | CT      | 8                | 1.1 (10 yrs)  |
|  | 871     | CT+RT   | 20               | 2.3 (10 yrs)  |
| Diehl <i>et al.</i> , 1998 <sup>34</sup>       | 403     | BEACOPP | 6                | 1.5 (3 yrs)   |

CR = cumulative risk; RT = radiotherapy; CT = chemotherapy; MOPP = mechlorethamine, oncovin, procarbazine, prednisone; ABVD = adriamycin, bleomycin, vinblastine, dacarbazine; COPP = cyclophosphamide, oncovin, procarbazine, prednisone; COMP = cyclophosphamide, oncovin, methotrexate, prednisone; OPPO = oncovin, procarbazine, prednisone, doxorubicin; BEACOPP = cyclophosphamide, oncovin, procarbazine, prednisone, bleomycin, etoposide, adriamycin.

bazine), do not seem to be associated with an increased risk of secondary leukemia.<sup>32,33</sup> New aggressive regimens including COPP plus bleomycin, etoposide and adriamycin (BEACOPP) probably carry higher risks.<sup>34</sup>

It remains controversial whether radiotherapy increases the leukemogenic risk associated with chemotherapy, although a recent meta-analysis supports this hypothesis.<sup>35</sup>

Radiotherapy certainly increases the risk of leukemia in patients previously treated with regimens including mechlorethamine and procarbazine (MOPP regimen) or lomustine; patients treated with extensive radiotherapy plus MOPP showed a higher risk of leukemia than those given limited radiotherapy plus MOPP.<sup>35-39</sup>

According to some reports<sup>31</sup> males and females appear to have similar risks of developing t-leukemia, but according to others the relative risk of leukemia is significantly greater in women.<sup>40</sup>

In patients previously treated with ABVD, radiotherapy probably does not increase the incidence of secondary leukemia.<sup>39</sup> In patients treated with MOPP-derived regimens excluding mechlorethamine, the addition of radiotherapy does not seem to increase the risk of leukemia much.<sup>39</sup>

### Non-Hodgkin's lymphoma

As in HD, alkylating agents are the major risk factors associated with t-AML for non-Hodgkin's lymphoma (NHL). Travis *et al.*<sup>41</sup> reported on a cohort study of 11,386 two-year survivors of NHL. Thirty-five patients with t-AML, were matched to 140 controls with NHL who did not develop AML. A significant excess of AML followed therapy with either prednimustine or regimens containing mechlorethamine and procarbazine. Elevated risks of leukemia following therapy with chlorambucil were restricted to patients given a cumulative dose of 1,300 mg or more. Cyclophosphamide regimens were associated with a small, but not significant, increased risk of AML. Radiotherapy given without alkylators was not linked to increased incidence of AML at any dosage. Other authors reported a higher incidence with a cumulative risk ranging between 4.6% and 8.0% at 10 years<sup>41-46</sup> (Table 4). In recent years only a few cases of AML following use of DNA topoisomerase II inhibitors have been reported in patients with NHL,<sup>47,48</sup> the increasing use of epipodophyllotoxins in the treatment of NHL would suggest that there will be an increased incidence of AML in this disease.

**Table 4. Risk of MDS/AML in patients receiving chemotherapy for non-Hodgkin's lymphoma.**

| References  | N. pts.           | MDS/AML (no.) | Cumulative risk of MDS/AML |
|---|-------------------|---------------|----------------------------|
| Greene <i>et al.</i> , 1983 <sup>42</sup>             | 517 CRT           | 9             | 7.9±3.2% (10 yrs)          |
| Pedersen-Bjergaard <i>et al.</i> , 1985 <sup>45</sup> | 602               | 9             | 8.0±3.3% (9 yrs)           |
| Ingram <i>et al.</i> , 1987 <sup>43</sup>             | 261 CRT           | 6             | 6% (7 yrs)                 |
| Lavey <i>et al.</i> , 1990 <sup>44</sup>              | 322 CT<br>292 CRT | 5<br>4        | 4.6% (10 yrs)              |
| Pui <i>et al.</i> , 1990 <sup>46</sup>                | 420               | 3             | 1.3% (10 yrs)              |
| Travis <i>et al.</i> , 1994 <sup>41</sup>             | 11,386            | 35            | 0.6% (10 yrs)              |

**Table 5. Risk of AML in patients receiving chemotherapy for acute lymphoblastic leukemia.**

| References                                   | N. pts. | MDS/AML (no.) | Cumulative risk of MDS/AML      |
|--|---------|---------------|---------------------------------|
| <b>Children</b>                              |         |               |                                 |
| Pui <i>et al.</i> , 1991 <sup>50</sup>       | 792     | 21            | 3.8% (6 yrs)                    |
| Neglia <i>et al.</i> , 1991 <sup>51</sup>    | 9720    | 2             | -                               |
| Kreissman <i>et al.</i> , 1992 <sup>52</sup> | 779     | 2             | 3.2%                            |
| Jankovic <i>et al.</i> , 1993 <sup>53</sup>  | 2334    | 6             | -                               |
| Winick <i>et al.</i> , 1993 <sup>54</sup>    | 205     | 10            | 5.9% (4 yrs)                    |
| <b>Adults</b>                                |         |               |                                 |
| Pagano <i>et al.</i> , 1998 <sup>55</sup>    | 942     | 4             | 0.59% (5 yrs)<br>3.63% (10 yrs) |

merase II inhibitors have been reported in patients with NHL,<sup>47,48</sup> the increasing use of epipodophyllotoxins in the treatment of NHL would suggest that there will be an increased incidence of AML in this disease.

### Acute lymphoblastic leukemia

In children cured of ALL, the risk of a t-AML has been evaluated in different series to be between 3.8% at 6 years and 5.9% at 4 years.<sup>49-55</sup> Pui *et al.* reported<sup>50</sup> that the risk of sAML was higher among ALL children who received a high cumulative dose of epipodophyllotoxins (>4,000 mg/m<sup>2</sup>) and prolonged epipodophyllotoxin therapy in weekly or twice-weekly doses. In adults a recent GIMEMA study demonstrated a low incidence of t-AML, which could be explained by the lower doses of epipodophyllotoxins administered in the various therapeutic approaches used for the treatment of adult ALL<sup>55</sup> (Table 5).

### Myeloma

The cumulative risk of secondary MDS/AML in myeloma was reported to be 17.4% at 50 months by Bergsagel *et al.*<sup>56</sup> and 10.0% at 8 years by Cuzick.<sup>57</sup> The most important determinant in increasing the risk of leukemia was the amount of melphalan the patients received. Patients treated with cyclophosphamide had a lower incidence of secondary leukemia without there being any relationship with the dose of cyclophosphamide.<sup>57</sup> Previous cumulative dose of alkylating agents was also the most important factor in determining MDS-AML development after autologous BMT.<sup>58</sup>

### Myeloproliferative disorders

In polycythemia vera and essential thrombocythemia, the risk of s-AML is related to type of therapy, being very high after radioactive phosphorus<sup>59</sup> (overall incidence of 10.3% at 10 years), and low after pipobroman.<sup>60-62</sup> In myelofibrosis with myeloid metaplasia the major risk factor is splenectomy.<sup>63</sup>

### Breast, ovarian and testicular neoplasms

In the past Carey *et al.* reported that patients with breast cancer surgically cured had a thirty-fold higher risk of a secondary AML than the general population.<sup>64,65</sup> Metcalf *et al.* showed in Wistar rats that intraperitoneal injection of methylcholanthrene caused acute leukemia or breast cancer indifferently, suggesting the possibility of a common etiological mechanism or at least a predisposing condition.<sup>66</sup> These data were not confirmed.<sup>67,68</sup> After melphalan-based adjuvant regimens in breast cancer a cumulative risk of AML of 0.7-1.68 at 10 years has been reported<sup>67-72</sup> (Table 6). The association of alkylating agents and topoisomerase II inhibitors seems to induce secondary leukemia with higher frequency, the cumulative risk at 3 years being 25±10%.<sup>69</sup>

Cyclophosphamide seems to be less leukemogenic,<sup>64</sup> indeed a recent prospective ECOG co-operative study on a large cohort of patients with breast cancer demonstrated that the use of a standard dose

**Table 6. Risk of MDS/AML in patients receiving chemotherapy for non-hematologic neoplasms.**

| References  | N. pts. | MDS/AML (no.) | Cumulative risk of MDS/AML |
|---|---------|---------------|----------------------------|
| <b>Breast cancer</b>                                  |         |               |                            |
| Fisher <i>et al.</i> , 1985 <sup>67</sup>             | 5,299   | 34            | 1.7±0.3% (10 yrs)          |
| Curtis <i>et al.</i> , 1990 <sup>68</sup>             | 13,734  | 24            | 0.7% (10 yrs)              |
| Andersson <i>et al.</i> , 1990 <sup>69</sup>          | 71      | 5             | 25.4±10.3% (37 months)     |
| Talmann <i>et al.</i> , 1995 <sup>70</sup>            | 2,638   | 5             | 0.2% (10 yrs)              |
| Diamandidou <i>et al.</i> , 1996 <sup>72</sup>        | 1,474   | 14            | 1.5% (10 yrs)              |
| <b>Ovarian cancer</b>                                 |         |               |                            |
| Pedersen-Bjergaard <i>et al.</i> , 1980 <sup>73</sup> | 553     | 7             | 7.6% (5 yrs)               |
| Greene <i>et al.</i> , 1986 <sup>42</sup>             | 1,179   | 21            | 8.6% (5 yrs)               |
| Travis <i>et al.</i> , 1999 <sup>76</sup>             | 28,971  | 90            |                            |
| <b>Testicular cancer</b>                              |         |               |                            |
| Travis <i>et al.</i> , 1997 <sup>78</sup>             | 28,843  | 27            |                            |
| Kallmannsberger <i>et al.</i> , 1998 <sup>79</sup>    | 302     | 4             | 1.3% (2 months)            |

of cyclophosphamide did not increase the risk of secondary AML in patients with early stage breast cancer,<sup>70</sup> whereas high doses of cyclophosphamide and doxorubicin seemed to be more dangerous<sup>71</sup> as did the combination of fluorouracil-doxorubicin-cyclophosphamide.<sup>72</sup> Radiotherapy can further enhance the risk of leukemia.<sup>68</sup>

The risk of t-AML in women treated for ovarian cancer has been demonstrated to be high,<sup>42,73,76</sup> particularly for those who received alkylating agents, in whom the risk is 7% at 10 years;<sup>74</sup> in those treated with platinum protocols,<sup>76</sup> the relative risk was about four-fold in relation to the cumulative dose and the type of platinum based compound utilized. However the risk is lower than that in patients treated with alkylating agents (relative risk = 40).

For patients treated for testicular cancer with chemotherapy including topoisomerase II inhibitors and cisplatin, a mean cumulative risk of 1.3 to 4.7% at 5 years was reported.<sup>74,77,79</sup> The risk of leukemia includes not only AML but also ALL with a five-fold relative risk increase.<sup>78</sup> A cumulative dose of etoposide > 2 g/sqm increases the risk.

### Secondary leukemia after transplantation procedures

High-dose chemotherapy followed by autologous bone marrow (ABMT) or peripheral stem cell transplantation is increasingly used in chemotherapy-sensitive malignancies, particularly in breast cancer, non-

**Table 7. Therapy-related leukemia following high dose chemo-radiotherapy and autologous bone marrow reinfusion for lymphoma.**

| Author, Center  | N. pts. transplanted | N. pts with t-MDS/AML | Actuarial incidence | Median latency |                |
|---|----------------------|-----------------------|---------------------|----------------|----------------|
|   |                      |                       |                     | from BMT       | from diagnosis |
| Darrington <i>et al.</i> , 1994 <sup>81</sup><br>Nebraska     | 511                  | 12                    | 4% (5yrs)           | 83 ms          | 44 ms          |
| Traweek <i>et al.</i> , 1994 <sup>82</sup><br>City of Hope    | 275                  | 10                    | 8-10% (7yrs)        | 3.9 yrs        | 1.4 yrs        |
| Stone <i>et al.</i> , 1994 <sup>83</sup><br>Dana-Farber       | 262                  | 20                    | 18±9% (6yrs)        | 69 ms          | 31 ms          |
| Miller <i>et al.</i> , 1994 <sup>84</sup><br>Minnesota        | 206                  | 9                     | 5±12% (6yrs)        | 5.4 yrs        | 34 yrs         |
| Millighan <i>et al.</i> , 1997 <sup>87</sup><br>EBMT          | 4459                 | 41                    | 2.5% (5 yrs)        | -              | -              |
| Pedersen <i>et al.</i> , 1997 <sup>88</sup><br>Rigshospitalet | 76                   | 6                     | 17.3% (6 yrs)       | -              | 4-43 ms        |
| Andrè <i>et al.</i> , 1998 <sup>89</sup><br>SFGM Paris        | 467                  | 8                     | 4.3% (5 yrs)        | -              | -              |
| Personal data, 1998   | 132                  | 0                     |                     | -              | -              |

Hodgkin's lymphoma, Hodgkin's disease, myeloma, and testicular and ovarian cancers.<sup>80</sup> Recent studies reported the development of myelodysplastic syndrome and s-AML in patients with Hodgkin's disease, non-Hodgkin's lymphoma and breast cancer after ABMT.<sup>81-87</sup>

In patients with lymphoma submitted to eradicating chemotherapy followed by BMT the cumulative risk has been estimated to range from 2.6% at 5 years to 17% at 6 years (Table 7).<sup>81-89</sup> In patients with breast cancer an actuarial incidence of secondary AML of 1.6% at 4 years has been reported.<sup>90</sup> In our experience we had only one case of secondary AML among 40 patients transplanted for ovarian and breast cancer. It remains unclear whether the risk of secondary MDS-AML is related to myeloablative therapies followed by stem cells infusion or to previous chemotherapy. Recent data support the hypothesis that previous therapy is the most important factor determining damage to hematopoietic stem cells favoring secondary leukemia.<sup>58,88,89</sup> In fact the incidence of secondary leukemia is very low in patients autotransplanted earlier<sup>90</sup> or submitted to allogeneic bone marrow transplantation.<sup>91</sup> Furthermore, in HD no difference in the incidence of secondary leukemias has been reported between grafted and ungrafted patients.<sup>89</sup>

### Secondary leukemia following another malignancy treated or not with chemo- and/or radiotherapy

Recently a study using the GIMEMA archive of adult acute leukemia, considered all registered leukemic patients with a history of previous malignancy.<sup>92</sup> From 1992 throughout 1996, 3,865 patients with a new diagnosis of acute leukemia, both myeloid and lymphoid, were registered. In 3,665 patients acute leukemia was diagnosed as a first malignancy, in 200 patients it was diagnosed as a second malignancy. Twenty-one patients had an ALL (2.3% of all ALL) and 179 patients had an AML (6% of all AML).

Among patients with s-AML, 67% were treated with chemo-radiotherapy, and 33% patients were treated with surgery only.

A comparative analysis of the two groups of patients, chemotherapy or surgery-treated, demonstrated that the latency between the diagnosis of the two malignancies was not different and the remission rate and the survival from diagnosis of s-AML were similar. Patients treated surgically only were older than patients treated with chemo-radiotherapy. Chromosome abnormalities involving chromosomes 5 and 7 were mostly present in patients treated with chemo-radiotherapy.

Considering the whole group of secondary AML collected in the study, it is interesting to note that more than 50% of secondary AML occurred in patients who had had three kinds of previous malignancies, breast cancer, NHL, and HD. An unusual frequency of acute

promyelocytic leukemia (APL) in these patients was also observed (15% of all secondary leukemias). It is noteworthy that in the Italian population secondary APL appears to be frequent, as reported in the international histiocytosis study.<sup>93</sup>

We can conclude that chemotherapy for a previous malignancy, particularly alkylating agents or topoisomerase II inhibitors, plays the most important role in the development of leukemia following a previous malignancy; but considering the high proportion of patients treated by surgery alone, the possibility that patients with cancer have an increased predisposition to leukemia cannot be excluded.

### Contributions and Acknowledgments

*GL was responsible for the conception of this review article and for the writing of the paper. All the authors contributed equally to the writing of the paper and its revision.*

### Funding

*This work was supported in part by a grant from MURST 40% (Università Cattolica, Rome, Italy).*

### Disclosures

*Conflict of interest: none.*

*Redundant publications: no substantial overlapping with previous papers.*

### Manuscript processing

*Manuscript received May 11, 1999; accepted July 7, 1999.*

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