Low incidence of secondary myelodysplasia and acute myeloid leukemia after high-dose chemotherapy as adjuvant therapy for breast cancer patients: a study by the Solid Tumors Working Party of the European Group for Blood and Marrow Transplantation

On behalf of the Solid Tumors Working Party of the European Group for Blood and Marrow Transplantation

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Background: To determine the incidence of secondary myelodysplasia (sMDS) or acute myeloid leukemia (AML) in node-positive breast cancer patients who received high-dose chemotherapy (HDCT) followed by autologous stem-cell support as adjuvant therapy.

Patients and methods: The incidence of sMDS/AML was retrospectively assessed in 364 node-positive breast cancer patients who received HDCT followed by autologous stem-cell support as adjuvant therapy between November 1989 and December 1997 and were reported to the European Group for Blood and Marrow Transplantation registry.

Results: The median age of the patients was 45 years (range 22–62 years). Two hundred and ninety-one patients received peripheral blood stem cells and 55 patients received autologous bone marrow as stem-cell support. The most frequently used conditioning regimen was the STAMP-V regimen (32%), followed by melphalan–thiotepa (22%) and melphalan–mitoxantrone–cyclophosphamide (21%). The 5-year probability of overall survival is 71% (95% CI 65% to 77%). After a median follow-up of 48 months (range 1–108 months) only one case of AML was observed, resulting in a crude incidence of 0.27%. This case of AML was observed 18 months after HDCT consisting of three cycles of epirubicin and cyclophosphamide with a cumulative dose of epirubicin 960 mg and cyclophosphamide 19 g. The French–American–British type of AML was M4, and the cytogenetic analysis showed a translocation t(9;11)(p22;q23). After complete remission following high-dose cytarabine and idarubicin the patient relapsed and died.

Conclusions: In contrast to patients with malignant lymphoma there seems to be no increased risk of sMDS/AML after HDCT in breast cancer. Continued monitoring is required to confirm this low incidence after a longer follow-up period.

Key words: acute myeloid leukemia, adjuvant therapy, breast cancer, high-dose chemotherapy, secondary myelodysplasia

Introduction
Secondary myelodysplasia (sMDS) or acute myeloid leukemia (AML) is a well-known long-term complication in patients who have received chemotherapy or radiation therapy for a previous malignancy [1–10]. During recent years the number of patients with hematological malignancies or solid tumors who received high-dose chemotherapy (HDCT) followed by autologous stem-cell support has increased substantially. While acute toxicities are well documented and the mortality of the procedure is rather low, clinical interest is focusing on long-term effects including the development of secondary leukemia.

Secondary MDS or AML has become a major problem for long-term survivors with lymphoid malignancies who have received a high-dose chemo/radiotherapy with autologous stem-cell support.

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Two different types of treatment-related leukemia can be distinguished. The first type results from prior therapy with alkylating agents or radiation therapy and occurs after a latency period of 5–7 years. This type of AML is often preceded by a preleukemic period of sMDS. Up to 90% of the patients with alkylating agent-related sMDS or AML show clonal chromosome aberrations, including monosomy or deletions on chromosomes 5 and/or 7, or complex aberrations involving chromosomes 3, 12, 17 and 21 [7]. The second type of therapy-related leukemia is induced by topoisomerase II targeted drug-like etoposide, anthracyclines or, recently, anthrancenediones [8–10]. This type of AML usually occurs after a median of 2 years and is not preceded by a myelodysplastic syndrome. According to the French–American–British (FAB) classification, more frequently M4 or M5 are observed and cytogenetic analysis shows a high frequency of rearrangements of chromosome band 11q23, t(8;21),t(15;17), inv(16) or t(8;16) as in de novo AML [8, 11]. Despite these more favorable chromosomal aberrations, the secondary leukemias have a poor prognosis. Secondary leukemia after treatment for breast cancer has been reported [12–17]. Specific risk factors were: a combination of chemotherapy and radiation therapy; cumulative doses of alkylating agents; and duration of therapy. The International Case Control Study reported a cumulative incidence of 0.7% for breast cancer patients treated with conventional chemotherapy and/or radiation therapy [13].

To date, only limited data have been published studying the risk of secondary leukemia in breast cancer patients who have received HDCT followed by autologous stem-cell transplantation [19–21]. Here we report the results of a retrospective study on the incidence of sMDS/AML after HDCT for primary breast cancer patients reported to the European Group for Blood and Marrow Transplantation (EBMT) registry.

### Materials and methods

#### Patient population and data collection

Patients (494) with node-positive breast cancer had received HDCT followed by autologous stem-cell transplantation as adjuvant therapy between November 1989 and December 1997 in 55 European centers and were reported to the EBMT registry. All centers received a questionnaire for the transplanted patients. Three hundred and sixty-four patients were evaluable to primary breast cancer patients reported to the European Group for Blood and Marrow Transplantation (EBMT) registry.

### Table 1. Conditioning regimens for high-dose chemotherapy

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin–cyclophosphamide-thiotepa (STAMP-V)</td>
<td>118 (32.4)</td>
</tr>
<tr>
<td>Melphalan–thiotepa</td>
<td>79 (21.8)</td>
</tr>
<tr>
<td>Mitoxantrone–melphalan–cyclophosphamide</td>
<td>75 (20.6)</td>
</tr>
<tr>
<td>Cyclophosphamide–methotrexate–epirubicin–paclitaxel–melphalan</td>
<td>16 (4.4)</td>
</tr>
<tr>
<td>Ifosfamide–cyclophosphamide–etoposide</td>
<td>16 (4.4)</td>
</tr>
<tr>
<td>Busulfan–melphalan–thiotepa</td>
<td>13 (3.6)</td>
</tr>
<tr>
<td>Carboplatin–cyclophosphamide–paclitaxel</td>
<td>8 (2.2)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>Epirubicin–cyclophosphamide × 3</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Others</td>
<td>27 (7.4)</td>
</tr>
<tr>
<td>Overall</td>
<td>364 (100)</td>
</tr>
</tbody>
</table>

source was bone marrow in 55 patients and peripheral blood stem cells in 309 patients. The median follow-up was 48 months (range 1–108 months).

### Statistical analysis

Time to sMDS/AML is the interval from HDCT to diagnosis of sMDS/AML. Patients who did not develop sMDS/AML were censored at date of death or at date of last follow-up for surviving patients. Data were updated as of October 2001. Time to sMDS/AML and the cumulative probability of developing sMDS/AML was estimated by the Kaplan–Meier method.

### Results

After a median follow-up of 48 months (range 1–108 months), one out of 364 patients developed secondary leukemia in this retrospective study. Thus, the crude incidence of secondary leukemia is 0.27%. The one case of AML was observed 18 months after a HDCT protocol consisting of three cycles of etoposide and cyclophosphamide with a cumulative dose of etoposide 960 mg and cyclophosphamide 19 g. The FAB type of AML was M4 and the cytogenetic analysis showed a translocation t(9;11)(p22;q23). After complete remission following high-dose cytarabine (ara-C) and idarubicin, the patient relapsed and died 12 months after diagnosis of AML (Tables 2 and 3).

### Discussion

This retrospective study suggests that HDCT supported by autologous stem-cell transplantation as adjuvant therapy in breast cancer patients results in a low probability of developing sMDS.

### Table 2. Patient characteristics

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Tumor stage</th>
<th>Estrogen receptor</th>
<th>High-dose regimen</th>
<th>Radiation therapy</th>
<th>Time from HDCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>T1N1a</td>
<td>Positive</td>
<td>Epirubicin–cyclophosphamide (IBCSG protocol 15/95)</td>
<td>60 Gy</td>
<td>18 months</td>
</tr>
</tbody>
</table>

HDCT, high-dose chemotherapy.
or AML with a crude incidence of 0.27%. The incidence of sMDS/AML does not seem be higher than that reported for conventional adjuvant chemotherapy (Table 4). In a large international case–control study the relative risk of developing sMDS/AML was 10 after conventional alkylating chemotherapy for breast cancer patients [13]. In this study, additional chest-wall irradiation appeared to increase the leukemogenic effect of chemotherapy (relative risk 17.4), and melphalan had a 10 times higher leukemogenic effect than cyclophosphamide. The higher leukemogenic risk of melphalan in the treatment of breast cancer was confirmed by the NSABP study, which reported an actuarial risk at 10 years of 1.7%, which was higher than the reported risk of 0.7% from the US cancer registry [12, 18].

A much lower incidence for sMDS/AML was reported for cyclophosphamide-based or combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF). The Milan group reported an actuarial risk at 10 years of 0.2% for leukemia after CMF treatment and a case–control study from Germany reported an actuarial risk at 10 years of 0.3% after cyclophosphamide-containing chemotherapy [16, 22]. More recently, some studies reported an incidence of sMDS/AML up to 5% in breast cancer patients after adjuvant chemotherapy containing the anthracyclene derivative mitoxantrone, a topoisomerase II targeting drug [10, 14, 17, 23].

In our study, none of the 75 patients who received a mitoxantrone (≥40 mg/m²) based conditioning regimen prior to autologous stem-cell transplantation experienced sMDS or AML during follow-up. The only case of AML in our study occurred after three cycles of high-dose epirubicin and cyclophosphamide. The cumulative dose was epirubicin 960 mg and cyclophosphamide 19 g. Anthracyclines, especially doxorubicin or more recently epidoxorubicin, are now widely used in adjuvant and metastatic treatment of breast cancer. These agents are DNA–topoisomerase II inhibitors and similar to the epipodophyllotoxins usually developed in AML after a median of 2 years without a preceding period of sMDS. The FAB type is mostly M4 or M5 with balanced chromosomal translocation at 11q23 [11]. The estimated risk of developing AML at 10 years after doxorubicin-containing chemotherapy and radiotherapy was 2.5% and 2.7% in two retrospective studies [24, 25]. However, treatment with doxorubicin without radiotherapy had a 10-year risk of sMDS/AML of only 0.5%, which was significantly less than the combination of doxorubicin and radiotherapy ($P = 0.01$) [25].

High-dose epidoxorubicin in combination with cyclophosphamide was also associated with an increased risk of secondary leukemia in a Canadian study [26]. Recently, Bergh et al. [27] reported in a randomized study comparing HDCT plus autologous stem-cell support with a tailored dose of 5-fluorouracil, cyclophosphamide and epidoxorubicin for high-risk breast cancer patients an increased risk of sMDS/AML in the anthracycline-based group ($n = 9$), while no sMDS/AML was seen in the high-dose arm. Therefore, it can be argued that the case of AML observed in our study with the typical interval of 18 months, the FAB M4 morphology and the balanced translocation 11q23 might be more related to the anthracycline treatment than to the HDCT as such.

There are few reports of sMDS/AML following HDCT for breast cancer. The Duke University reported in 864 patients who

### Table 3. Characteristics of an acute myeloid leukemia (AML) patient

<table>
<thead>
<tr>
<th>Type of AML</th>
<th>Cytogenetics</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Time from sMDS to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>M4</td>
<td>t(9;11)(p22;q23)</td>
<td>Ara-C–idarubicin</td>
<td>Relapse/died</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Ara-C, cytarabine; sMDS, secondary myelodysplasia.

### Table 4. Studies of sMDS/AML in breast cancer patients after conventional and high-dose chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>sMDS/AML</th>
<th>Actuarial risk (%)</th>
<th>Chemo/radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtis et al. [12]</td>
<td>13734</td>
<td>24</td>
<td>0.7</td>
<td>Different conventional regimens</td>
</tr>
<tr>
<td>Fisher et al. [18]</td>
<td>5299</td>
<td>34</td>
<td>1.7</td>
<td>Melphalan-based conventional therapy</td>
</tr>
<tr>
<td>Valagussa et al. [22]</td>
<td>2465</td>
<td>3</td>
<td>0.2</td>
<td>CMF conventional therapy</td>
</tr>
<tr>
<td>Haas et al. [16]</td>
<td>n.e.</td>
<td>52</td>
<td>0.3*</td>
<td>Cyclophosphamide-based conventional therapy</td>
</tr>
<tr>
<td>Saso et al. [17]</td>
<td>1774</td>
<td>9</td>
<td>1.6</td>
<td>Mitoxantrone-based conventional therapy</td>
</tr>
<tr>
<td>Linassier et al. [10]</td>
<td>350</td>
<td>2</td>
<td>0.7</td>
<td>Mitoxantrone-based conventional therapy</td>
</tr>
<tr>
<td>Diamandidou et al. [25]</td>
<td>1474</td>
<td>14</td>
<td>1.5</td>
<td>Doxorubicin-based conventional therapy</td>
</tr>
<tr>
<td>Laughlin et al. [19]</td>
<td>864</td>
<td>5</td>
<td>1.6</td>
<td>High-dose therapy: carmustine–cyclophosphamide–cisplatinum</td>
</tr>
<tr>
<td>Martinez-Climent et al. [21]</td>
<td>229</td>
<td>0</td>
<td>0</td>
<td>High-dose therapy: STAMP-V</td>
</tr>
<tr>
<td>EBMT study</td>
<td>364</td>
<td>1</td>
<td>0.3</td>
<td>Different high-dose regimens</td>
</tr>
</tbody>
</table>

*Estimated risk/case–control study.

AML, acute myeloid leukemia; CMF, combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil; EBMT, European Group for Blood and Marrow Transplantation; sMDS, secondary myelodysplasia; n.e., not evaluable.
received a high-dose regimen consisting of carmustine, cyclophosphamide and cisplatinum a 4-year probability of developing sMDS/AML of 1.6% [19]. In a Spanish trial involving 229 patients after a median follow-up of 36 months, no case of sMDS/AML was observed [21]. In that trial, in some patients (5%) cytogenetic aberrations were found after HDCT, but these aberrations were only transient and disappeared without developing sMDS or AML. These findings, as well as our data, do not support the hypothesis that HDCT increases the risk of developing sMDS/AML in breast cancer patients. However, these results are in contrast to the reported probability of 14–18% at 5 years after autologous transplantation for lymphoma patients [4–6]. Risk factors such as age, a higher cumulative dose of alkylating agents or previous radiotherapy, particularly the use of total-body irradiation as conditioning regimen, may have caused the higher incidence in lymphoma patients [3–6]. However, since it remains unclear whether prior chemotherapy, the type of conditioning regimen or the reinfusion of preleukemic progenitor cells during transplantation causes sMDS/AML, the observed difference in sMDS/AML between lymphoma and breast cancer patients after HDCT is unclear.

We conclude that sMDS/AML is a rare but potential complication following HDCT and autologous stem-cell support in breast cancer patients. The incidence is low compared with the incidence in patients with malignant lymphoma who underwent autologous transplantation. Longer follow-up is necessary to determine late occurrence of sMDS/AML.

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