Breast cancer in Hodgkin’s disease and non-Hodgkin’s lymphoma survivors

G. Sanna1*, K. Lorizzo1, N. Rotmensz2, V. Bagnardi2,4, S. Cinieri3, M. Colleoni1, F. Nole1 & A. Goldhirsch1

1European Institute of Oncology, Medical Oncology; 2European Institute of Oncology, Epidemiology and Biostatistics; 3European Institute of Oncology, Haematology; 4Department of Statistics, University of Milan-Bicocca, Milan, Italy

Received 20 June 2006; revised 15 September 2006; accepted 18 September 2006

Background: Better therapeutic approaches for patients with Hodgkin’s disease (HD) and non-Hodgkin’s lymphomas (NHL) resulted in high cure rates, at cost of serious late side effects. Second primary tumours are a major concern for long-term survivors, and breast cancer (BC) is the most common solid tumour among women treated for HD.

Materials and methods: Fifty-three women treated for primary BC with previous history of malignant lymphoma were identified in our institution, 35 with HD (66%), 18 (34%) with NHL. A comparison group was randomly selected from our database matching for each patient with previous lymphoma, two patients with primary BC (rate 1 : 2) for age, stage (pathological tumour size [pT] status and nodal status), year of diagnosis, and estrogen and progesterone status (positive versus negative). The primary end points were disease-free survival (DFS) and overall survival (OS).

Results: The two groups of patients were compared for biological features: histopathological diagnosis, grading, lymphatic invasion, c-erbB2 overexpression, and Ki-67. Considering these variables, no significant differences were observed between the two groups with the exception of Ki-67, which was found higher in those with previous HD or NHL (65% versus 49%, respectively, \( P = 0.0526 \), borderline significant). Comparing the two groups for treatment approach, no differences were found for surgical and medical therapy (endocrine therapy and chemotherapy). However, regarding patients with node-positive disease (14 versus 35 patients), five patients in the lymphoma group (36%), compared with 24 (69%) in the matched group received anthracycline-based therapy (\( P = 0.0345 \)). As expected, radiotherapy was used very differently in the two groups, with 36% of patients in the study group undergoing intraoperative radiotherapy with electrons versus 10% in the control group (\( P = 0.0001 \)). Five-year DFS was 54.5% for the study cohort compared with 91% for controls (\( P < 0.0001 \)). Five-year OS percentages were also statistically different (86.6% and 98.6%, respectively, \( P = 0.031 \)).

Conclusions: Previous history of malignant lymphoma is a negative prognostic factor for women diagnosed subsequently with BC. Some undertreatment of women with the latter might be hypothesised as the reason for the worse outcome. Influence of other variables, like previous exposure to cytotoxics, or some unknown biological features related to the previous disease and treatment, should still be investigated in the attempt to improve the dire outcome of these patients.

Key words: breast cancer, Hodgkin’s disease, non-Hodgkin’s lymphoma
The incidence of non-Hodgkin's lymphoma (NHL) has increased during the past 40 years in most Western countries [18, 19]. Life expectancy of patients with NHL has improved, result of better treatments, thus increasing the risk of second malignancies in long-term survivors [20]. In this population, information is scarce on second malignancies in general, and on BC in particular.

In several NHL cohorts, a reduction in BC risk was observed. This was described as statistically significant only in a few studies [21–26]. As previously reported, drugs commonly used also in NHL can lead to ovarian suppression, with an endocrine effect in the development of breast tumours [27].

Most of the studies conducted among long-term survivors after HD and NHL described the relative risk of developing second cancers after multimodal treatments. The estimated actuarial incidence of any second neoplasm 15 years after the diagnosis of HD was 7.0% (95% CI, 5.2 to 8.8% [8].

In our study, we identified patients who were referred to our institution for treatment of breast with the history of treated and cured malignant lymphoma.

With the aim to better understand the features of BC in HD and NHL survivors, choice of procedures of care and related prognosis, we evaluated features of BC in HD and NHL survivors in comparison with BC in a matched control group of patients selected among women referred to the same institute.

materials and methods

From February 1997 to September 2005, 53 patients with a history of lymphoma were referred to our institute for primary BC. Thirty-five patients had had a previous diagnosis of HD (66%) and 18 (34%) of NHL were treated to complete remission of the disease.

All records were reviewed retrospectively. The patients in the control group were selected from all BC women undergone surgery during the same period in the same institution. For each case, we selected two matched patients who did not have a previous lymphoma.

The variables used to make the randomly assigned matches were as follows:
• Age (within 5 years)
• Year of diagnosis (within 2 years)
• Tumours size
• Nodal status 0, 1–3, >3 involved nodes
• Steroid hormone receptors [estrogen receptor (ER) and progesterone receptor (PgR)] (positive versus negative). An immunohistochemical staining in at least 10% of tumour cells was considered positive.

If an exact match was possible on all the five variables, we relaxed the criteria to only four, attempting to select a comparison patient with a less favourable prognosis (more positive nodes, bigger tumour size, negative receptors, and younger age at diagnosis). For two patients, we were able to match only one woman, leading to a comparison group of 103 patients.

Events were retrospectively identified from routine follow-up data. In case of unavailability of a clinical examination during the time frame of the study conduct, the patient was contacted by telephone. If death occurred, the date was ascertained by the registry office.

statistical methods

The chi-square test was used to assess differences between the study group and the comparison group in the distribution of prognostic variables and treatment approaches.

The primary end points were DFS and overall survival (OS). DFS was calculated from the date of surgery to any relapse, the appearance of a second primary cancer, or death, whichever occurred first.

OS was defined as the time interval from the date of surgery to death from any cause.

Survival curves for study and comparison groups were estimated using the Kaplan–Meier method [28]. The log-rank test was used to assess the survival difference between the two groups. A multivariate Cox proportional hazards model [29] was fitted to assess the independent prognostic significance of a previous lymphoma on DFS, controlling for matching variables and prognostic factors differently distributed between the two groups.

All analyses were carried out with the SAS software (SAS Institute, Cary, NC). All tests were two sided.

results

patient characteristics (study group)

Median age at diagnosis of HD was 22 years (range 13–49) and the mean interval to BC diagnosis was 19 years (range 5–46). For women with previous NHL, median age at diagnosis of lymphoma was 46 years (18–73) and the median time to BC occurrence was of 8.5 years (range 0–23).

Treatment of lymphomas consisted of radiotherapy alone, chemotherapy alone, or combined chemoradiotherapy.

Among patients with previous HD, 11 patients received only radiotherapy (31%), two patients chemotherapy (6%), and 22 patients (63%) a multimodality approach.

In the group of NHL, two women (12%) underwent radiotherapy, six (38%), chemotherapy, and the majority (eight patients, 50%) a combined treatment. After lymphoma diagnosis, 21 patients (40%) had one or more pregnancies, revealing that at least in these women ovarian function was maintained despite treatments.

Surgery was predominately conservative, with 18 (47%) patients undergoing quadrantectomy (QUAD) plus intraoperative radiotherapy with electrons (ELIOT), 15 patients lumpectomy plus complementary external beam irradiation, and five patients QUAD without complementary radiotherapy. Mastectomy was carried out in 14 patients, with one case of nipple-sparing mastectomy and ELIOT.

Previous radiotherapy field influenced the subsequent local treatment of BC; patients who did not receive radiotherapy for lymphomas underwent more frequently conventional radiotherapy for BC (62%), compared with women who did carry out previous radiotherapy (24%). In the latter subgroup, the majority of patients received ELIOT.

comparison with the matched group

The matched groups of patients were compared for different features: familiarity, medical treatment, surgical treatment, histopathological diagnosis, grading, lymphatic invasion, c-erbB2 overexpression, and Ki-67 (Table 1).

Most of the tumours were ER/PgR positive (72% in the study group and 77% in the control group), pT1 tumours at diagnosis (70% versus 74%), and nodal negative (35% versus 55%).

Considering biological variables, no significant differences were found between the two groups with the exception of
proliferation index (Ki-67) which was found higher in the study group ($P = 0.0526$).

Regarding BC treatment, we stratified patients for age (≤40 years and >40 years) and no differences were observed in the surgical and medical approaches (chemotherapy and hormonal treatment).

In the subgroup of patients with node-positive disease (14 versus 35 patients), five women out of 14 in the study group (36%), compared with 24 out of 35 (69%) in the matched one, however, received anthracycline-based therapy ($P = 0.0345$).

Radiotherapy was used very differently, with 36% of patients in the study group receiving ELIOT versus 10% in the control group ($P = 0.0001$).

Follow-up data are available for 52 patients in the lymphoma group and for 103 patients in the control group.

The median follow-up from initial BC diagnosis was 41 months (range 1–101).

We observed 15 events in the lymphoma cohort (29%), compared with seven in the matched one (7%) with a 5-year DFS of 54.5% and 91%, respectively ($P < 0.0001$, Figure 1). In the study group, three patients experienced locoregional events (second BC or local relapse), six cases (50%) distant metastases, and three cases second primary carcinomas other than breast carcinoma. In the control group, three locoregional relapse (controlateral or ipsilateral breast tumour), one case of distant metastases (20%), and one case of second primary carcinoma were observed.

The Cox proportional hazards regression model, controlling for matching variables and proliferation index, yielded a hazard ratio of 9.4 (95% CI 3.0–29.1) for the study group compared to the matched group.

Six patients died in the lymphoma cohort, four due to BC and two from unknown causes. In the matched group, one patient died for disease progression and one for other causes. Five-year OS was also significantly different (86.6% versus 98.6%, respectively, $P = 0.031$, Figure 2).

**discussion**

Better therapeutic approach in the treatment of patients with HD and NHL have led to high cure rate, with serious late effects of therapy, in particular second primary tumours, being a major concern in long-term survivors.

Several studies have reported an increased risk of development of BC in women with previous diagnosis of HD. For an HD survivor who was treated at an age of 25 years with a chest irradiation dose of at least 40 Gy without alkylating agents, estimated cumulative risk of BC by age 35, 45, and 55 years were 1.4%, 11.1%, and 29%, respectively [16]. Assessment of late effects in a cohort of female HD patients treated with mantle radiotherapy identified from a database concerning BC screening recall showed high mortality and frequent undiagnosed abnormalities in tissues within radiotherapy field [21].

Multiagent chemotherapy with alkylating drugs in HD and NHL apparently protects from BC, possibly related to

### Table 1. Characteristics of patients with previous diagnosis of lymphoma (study group) and their comparison group (no matching variables)

<table>
<thead>
<tr>
<th></th>
<th>Study group ($n = 53$)</th>
<th>Comparison group ($n = 103$)</th>
<th>$P$ value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familiarity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>24</td>
<td>0.6404</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>20</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Medical treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary chemotherapy</td>
<td>2</td>
<td>4</td>
<td>0.3352</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>42</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>38</td>
<td>72</td>
<td>0.4105</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>15</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Histological classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma</td>
<td>43</td>
<td>81</td>
<td>0.3036</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>7</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Grading</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>13</td>
<td>0.2226</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphatic invasion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>34</td>
<td>71</td>
<td>0.9073</td>
</tr>
<tr>
<td>Present</td>
<td>14</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Ki-67</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>17</td>
<td>35</td>
<td>0.0526</td>
</tr>
<tr>
<td>≥20%</td>
<td>32</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>CerbB-2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overexpressed</td>
<td>6</td>
<td>16</td>
<td>0.9034</td>
</tr>
<tr>
<td>Not overexpressed</td>
<td>32</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>15</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Chi-square test.
cytotoxics-induced ovarian function suppression in young women [22–27].

Up to date, the majority of retrospective studies conducted among long-term survivors after HD and NHL were designed to quantify the relative risk of developing second malignancies. These results may be useful in defining specific guidelines of follow-up, leading eventually to secondary prevention (early diagnosis). A recent work concerning BC screening in women surviving HD indicates that providing risk information may encourage cancer survivors to take health preventive actions [30]. In patients treated for HD, breast cancer was the most common solid tumour (standardized incidence ratio 75.3; 95% CI, 44.9 to 118.4), with an estimated actuarial incidence in women that approached 35% (95% CI, 17.4 to 52.6%) by 40 years of age [8].

We conducted a retrospective study with the aim of defining clinical history, pathological features, and prognosis of BC arising in patients with previous lymphoma.

The primary end points were DFS and OS.

Evaluating the biological characteristics of the tumour, only the proliferation index was found to be higher in the study group compared with the control group (Ki-67 ≥20% was 65% versus 49%, with chi-square P value of 0.0526, borderline significant). We do not know how this observation should be interpreted, and may be simply related to constitutive aggressiveness of BC developing in lymphoma patients.

As expected, radiotherapy was used very differently in the two groups, related to previous field irradiation. The incidence of local relapse is under 5% in the lymphoma cohort indicating that conservative surgery plus EIOT radiotherapy may be a valid alternative to radical mastectomy. Recently, EIOT has been described as a new option for early BC patients previously treated for HD [31].

On the other side, no significant differences were found in systemic therapies (rate of patients receiving neo-adjuvant and adjuvant chemotherapy, endocrine therapy, and immunotherapy) and surgical treatments.

However, despite anthracycline-based therapy being the standard adjuvant option for patients with nodal involvement [32, 33], only five patients out of 14 in the study group (36%), compared with 24 out of 35 (69%) in the comparison, one received anthracycline-containing regimens (P = 0.0345).

Considering the DFS, we found a high statistical significant difference between the two cohorts (5-year DFS 54.5% and 91%, respectively, with a log-rank P < 0.0001), with a particular higher incidence of distant metastases in the lymphoma group (six events versus one). Despite different initial therapies for HD and NHL, the DFS was similar in these two groups (5-year DFS: 50.2% versus 63.5%, respectively, P = 0.9016).

Five-year OS percentage was also significantly different (86.6% versus 98.6%, respectively, P = 0.0031).

These results indicate that previous history of malignant lymphoma is a negative prognostic factor for women diagnosed subsequently with BC. The reduced use of anthracyclines in the adjuvant setting might be hypothesised as the reason for the worse outcome. In addition, even the presence of higher grades (though not significant) might account for the poorer prognosis of the lymphoma cohort. The vast majority of women have already undergone multiagent systemic chemotherapy and/or chest radiotherapy, eventually leading to accumulation of genetic damage that may determine resistance to further treatments. In these patients, genetic factors and eventually differences in the immunitary status might also be considered.

Influence of other variables, or some unknown biological features related to the previous disease and treatment, should still be investigated in an attempt to improve the dire outcome of these patients.

references


