Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha

Peter McLaughlin, Elihu Estey, Armand Glassman, Jorge Ramoguera, Felipe Samaniego, Ana Ayala, Kimberly Hayes, Anne Marie Maddox, H. Alejandro Preti, and Fredrick B. Hagemeister

Treatment-related myelodysplasia (t-MDS) occurs less frequently with the nucleoside analogs than with DNA-damaging agents such as alkylators or topoisomerase II inhibitors. In a chemoimmunotherapy trial conducted between 1997 and 2003 in patients with stage IV indolent lymphoma, 202 patients were treated and 8 have developed MDS between 1 and 5 years after therapy, including 4 who received only fludarabine, mitoxantrone, and dexamethasone (FND) for 6 to 8 courses, with or without rituximab, followed by interferon alpha (IFN-α). Complex cytogenetic abnormalities were present in all patients. Abnormalities of chromosome 7 were present in 6 of the 8 patients, 3 of whom received only FND ± rituximab and IFN-α. The abnormalities of chromosome 7 were monosomy 7 in 4 patients (1 of which had add 7p in the remaining chromosome); 1 del 7q; and 1 der 7. MDS with features classically associated with DNA-damaging agents can occur following therapy with FND, with or without rituximab, and IFN-α. (Blood. 2005;105:4573-4575)

© 2005 by The American Society of Hematology

Introduction

Alkylating agent therapy does not cure patients with indolent lymphoma and can result in late morbidity such as treatment-related myelodysplasia (t-MDS). Alternatives to alkylators include biologic agents and purine nucleoside analogs, which have a low reported frequency of t-MDS.

The combination of fludarabine, mitoxantrone, and dexamethasone (FND) is an effective regimen for patients with indolent lymphoma. Recently, we combined rituximab with FND, either concurrently (R-FND) or sequentially (FND→R), followed by interferon alpha (IFN-α) maintenance, for patients with stage IV indolent lymphoma. Preliminary reports have described good short-term safety and efficacy of this program, including a 3-year failure-free survival rate of greater than 65% and a 3-year survival rate of 95%.

The current report describes the occurrence of t-MDS in 8 patients in this trial.

Patients and methods

Patients

From 1997 to 2003, 202 evaluable patients with stage IV indolent lymphoma were treated on this trial; all signed informed consent in accordance with the University of Texas M.D. Anderson Cancer Center institutional review board regulations and the Declaration of Helsinki. With a median follow-up of 42 months (range, 6-70 months), 8 patients have been diagnosed with t-MDS or treatment-related acute myeloid leukemia (t-AML).

The lymphoma protocol included FND for the majority of patients, either concurrently with rituximab or followed by rituximab. Patients also received IFN-α maintenance. The doses of FND were as follows: fludarabine 25 mg/m² intravenously days 1 to 3, mitoxantrone 10 mg/m² intravenously on day 1, and dexamethasone 20 mg orally or intravenously days 1 to 5, every 4 weeks for 8 cycles. In R-FND, rituximab 375 mg/m² was given intravenously on days 1 and 8 of course 1; in courses 2 to 5, it was given on day 1 only. Responding patients received maintenance with 3 million units/m² interferon alpha 2b subcutaneously daily on days 2 to 14 and dexamethasone 40 mg orally on days 1 to 3, given monthly for 1 year. In FND→R, rituximab 375 mg/m² was given intravenously once monthly for 6 doses, starting at month 12.

Patients with follicular lymphoma without BCL2 gene rearrangement received alternating triple therapy (ATT) with concurrent rituximab, followed by maintenance IFN-α. ATT is a rotation of 3 regimens, CHOD-Bleo (cyclophosphamide, doxorubicin, vincristine, dexamethasone, bleomycin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), and NOPP (mitoxantrone, vincristine, prednisone, procarbazine), for 12 courses (3-4 courses of each); doses have previously been reported. Six doses of rituximab (375 mg/m²) were included with ATT: 2 in courses 1 and 3 and 1 dose in courses 4 and 6.

Diagnosis of t-MDS and t-AML

The diagnosis of t-MDS, using World Health Organization criteria, was considered when the bone marrow contained excess blasts (> 5%) or was dysplastic or when unexpected cytopenias occurred. Marrow assessment was done pretreatment and every 3 to 6 months if initially positive. However, neither pretreatment nor follow-up cytogenetic monitoring was part of the study design; cytogenetics was performed only when MDS was
Table 1. Features of myelodysplasia and/or leukemia

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient age, y</th>
<th>Latent period, mo</th>
<th>Protocol arm</th>
<th>Type of MDS</th>
<th>Cytogenetics</th>
<th>Metaphases abnormal/diploid</th>
<th>Therapy for MDS/AML</th>
<th>Survival after MDS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>15</td>
<td>FND→R</td>
<td>RARS</td>
<td>42-46, X, del (X) (q22), del (1) (p34), –3, del (3) (p21), add (5) (q35), +6, der (7) (t7;7) (q36;q11), –8, –10, –11, del (11) (p11.2), del (12) (p11.2), del (15) (t5;15) (q11;p13), add (17) (p11), +t-7mar [cp20]</td>
<td>20/0</td>
<td>CSFs</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>34</td>
<td>R-FND</td>
<td>RAEB</td>
<td>45, X, t(3;21) (q26;q22), –7 [10]</td>
<td>10/10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>54</td>
<td>R-FND</td>
<td>RARS</td>
<td>46, XY, –7, del (12) (p11p12), +mar [19]</td>
<td>19/1</td>
<td>CSFs</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>28</td>
<td>R-FND</td>
<td>MDS</td>
<td>46, XX, del (13) (q12q14) [5]</td>
<td>11/9</td>
<td>CSFs</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>57</td>
<td>R-FND*</td>
<td>AMMoL</td>
<td>46, XY, del (5) (q31q35), del (7) (q22q34), del (12) (p11p12) [20]</td>
<td>20/0</td>
<td>Chemo</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>31</td>
<td>ATT†</td>
<td>RAEB</td>
<td>48, XX, +8, t(16;21) (q24;q21), +18 [18]</td>
<td>18/2</td>
<td>Chemo; BMT</td>
<td>11+</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>59</td>
<td>ATT</td>
<td>R-FND</td>
<td>46, XY, –2, dup (2) (q21q31), –5, add (17) (p13), +mar [3]</td>
<td>12/8</td>
<td>Chemo; BMT</td>
<td>10</td>
</tr>
</tbody>
</table>

FND→R indicates fludarabine, mitoxantrone, dexamethasone (FND) followed by rituximab (and interferon) maintenance; RARS, refractory anemia with ringed sideroblasts; CSFs, colony-stimulating factors (including erythropoietin); R-FND, concurrent rituximab and FND; RAEB, refractory anemia with excess blasts; MDS, myelodysplasia that was not precisely categorized morphologically; AMMol, acute myelomonocytic leukemia; chemo, chemotherapy; ATT, alternating triple therapy (see "Patients and methods"); and BMT, allogeneic marrow/stem cell transplantation.

*Additional interventions before AMMol included splenectomy and R-CHOP.
†One course of R-FND before change to ATT.
‡Therapy also included one course of salvage R-CHOP before AML.

Statistical analysis

The time to development of t-MDS was measured from the time of lymphoma therapy until the t-MDS diagnosis. The actuarial incidence was calculated by the method of Kaplan and Meier.11

Results

Eight of 202 patients developed t-MDS or t-AML (crude incidence 4%), as categorized in Table 1. In all cases, the t-MDS was first suspected based on cytopenias (n = 7) or overt leukemia (n = 1) on routine hematolgy survey. The median age of the MDS patients was 57 years (range, 42-75 years), with 3 males and 5 females. MDS was diagnosed a median of 32 months after the lymphoma therapy (range, 15-59 months). Figure 1 shows the actuarial incidence of t-MDS.

The initial lymphoma treatment for these 8 patients included R-FND for 5, FND→R for 1, and ATT→R for 2 (Table 1). Two R-FND patients who attained only partial remission received salvage therapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) before developing t-MDS. The other 6 patients attained complete remission (CR) with the lymphoma therapy. One patient was still on IFN-α maintenance when MDS was diagnosed, 5 others were off therapy 12 to 40 months. Five patients were in ongoing CR from the lymphoma standpoint when the t-MDS was diagnosed.

All had cytogenetic abnormalities commonly seen following alkylating agent therapy, including abnormalities of chromosome 5 and/or 7 in 6 patients (Table 1). Two patients had del(12)(p11p12). None had abnormalities of 11q23.

The median survival after the development of AML or MDS was 9 months (range, 2-17 months).

Discussion

Management options for indolent lymphoma are numerous. The risks of the lymphoma need to be weighed against those of the

Figure 1. Actuarial incidence of t-MDS. (A) Actuarial incidence of t-MDS (and 95% confidence interval [CI]) for the entire study population. At 4 years the risk is 3% (CI 1%-7%). (B) Actuarial incidence of t-MDS by treatment arm. At 4 years the risk (and 95% CI) by regimen is ATT, 3% (0.4%-21%); FND→R, 1% (0.2%-9%); and R-FND, 4% (1%-13%). When the 2 FND arms are pooled, the risk is 3% (1%-7%).

From www.bloodjournal.org by guest on April 14, 2017. For personal use only.
therapy. In our stage IV protocol, a risk-adapted approach was taken, with ATT reserved for those considered to be poor risk.\(^8\) MDS has been previously described following ATT.\(^4\)

The risk of t-MDS in patients who received only FND, IFN-\(\alpha\), and rituximab was expected to be minimal. MDS has been described rarely following IFN-\(\alpha\),\(^12\) never with rituximab, and only infrequently with the nucleoside analogs or other antimetabolites.\(^2,13-16\) Mitoxantrone is an intercalator and a topoisomerase II inhibitor, which has only infrequently been associated with MDS.\(^17\) MDS can occur following CHOP-like therapy,\(^18\) which is a potentially confounding factor in 2 of our patients who received R-CHOP salvage therapy; it is plausible to suspect that the primary therapy contributed to the risk of MDS in those cases.\(^19\)

The cytogenetic abnormalities in these patients were complex (Table 1). Six patients had abnormalities of chromosome 7, as commonly observed following exposure to DNA-damaging agents. Two patients had del(12)(p11p12). Abnormalities of chromosome 12 are seen in a broad spectrum of hematologic malignancies, including in secondary leukemias after mutagenic agents, and are generally associated with a poor outlook.\(^20\) The 11q23 abnormality, classically observed with topoisomerase II inhibitors, was not observed in our cases.\(^21\)

Fludarabine inhibits the DNA repair process, thereby enhancing the antineoplastic effect of an agent like cyclophosphamide.\(^22\) This synergy has been exploited successfully in the treatment of chronic lymphocytic leukemia (CLL); an analogous synergy may exist for fludarabine and mitoxantrone. But there could also be augmented adverse effects. MDS has been reported following fludarabine plus chlorambucil for CLL.\(^23\) Antitumor synergy exists between rituximab and several chemotherapeutic agents,\(^24\) but rituximab selectively targets B cells so an impact on myeloid cells would not be expected.

The risk of t-MDS is calculated variably in the literature: crude incidence figures (4% in our report) underestimate the risk, whereas Kaplan-Meier plots (as in Figure 1) overestimate the risk.\(^25\) Overall, up to 10% of lymphoma patients treated with standard chemotherapy may develop t-MDS.\(^26\) Prolonged exposure to cytotoxic agents increases the risk. Patients in the current report received 6 to 8 courses of FND or 9 to 12 courses of ATT. Shorter-duration therapy might lessen the risk. Others who use 4 to 6 courses of FND and variants in the front-line setting have not noted a high frequency of t-MDS (E. Montserrat, J. Seymour, V. Jain, P.L. Zinzani, W. Hiddemann, S. Gregory, personal communications, July 2004). Since t-MDS following FND with or without rituximab and IFN-\(\alpha\) appears to be infrequent, routine cytogenetic monitoring may not be warranted. But based on the current report, t-MDS occurring 1 to 5 years after therapy must be considered a risk of FND or R-FND plus IFN-\(\alpha\) therapy, particularly if protracted treatment is given.

Acknowledgments

The authors thank Joyce Palmer-Brown for preparation and editing of the manuscript and Mark Hess for the Kaplan-Meier curves.

References

Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha

Peter McLaughlin, Elihu Estey, Armand Glassman, Jorge Romaguera, Felipe Samaniego, Ana Ayala, Kimberly Hayes, Anne Marie Maddox, H. Alejandro Preti and Fredrick B. Hagemeister