Chromosome Aberrations and Prognostic Factors in Therapy-Related Myelodysplasia and Acute Nonlymphocytic Leukemia

By Jens Pedersen-Bjergaard, Preben Philip, Severin Olesen Larsen, Grethe Jensen, and Karin Byrsting

Cytogenetic studies of 91 consecutive patients with therapy-related myelodysplasia or overt acute nonlymphocytic leukemia disclosed characteristic defects of chromosome 7 in 48 cases and of chromosome 5 in 21 cases. The chromosome 5 abnormalities were consistently present in all abnormal mitoses at the time of diagnosis, as were the chromosome 7 abnormalities in 45 of the 48 patients. Various abnormalities, primarily of the short arm of chromosome 17, were observed in 13 cases, abnormalities of the long arm of chromosome 21 were observed in 12 cases, and rearrangements of 11q23 were seen in nine cases. Thirteen patients presented a normal karyotype. Previous therapy with alkylating agents, the presence of an initial myelodysplastic phase, and abnormalities of chromosome 7 or 5 were interdependent. Patients with 11q23 rearrangement typically developed overt leukemia of FAB types M4 or M5a without myelodysplasia and with a short latent period. Evaluated by Cox regression analysis, complete remission of the primary malignancy and a malignant lymphoma as primary tumor were the two most important and independent prognostic factors indicating a longer survival \( (P = .008) \). In addition, the platelet count at diagnosis was a significant prognostic factor \( (P = .01) \). For the subgroup of 62 patients with myelodysplasia, the number of chromosome aberrations, the percentage of blasts in the bone marrow, and the hemoglobin level were other significant and independent prognostic factors \( (P = .05, .05, \text{and} .004, \text{respectively}) \). The most important predictive factor for a favorable response to intensive antileukemic chemotherapy in overt leukemia was the absence of a preceding myelodysplastic phase \( (P = .0014) \).

For many years therapy-related myelodysplasia (t-MDS) and therapy-related acute nonlymphocytic leukemia (t-ANLL) have been recognized as the most serious long-term complications of current cancer therapy. In previous studies of patients with Hodgkin’s disease, advanced age has been identified as the predominant predisposing factor.\(^1,3\) As in many other types of tumor, treatment with alkylating agents has been disclosed as the most important direct causal factor.\(^1,4\)

Other concurrent studies have discussed the characteristic chromosome abnormalities observed in 80% to 90% of patients with t-MDS or t-ANLL.\(^7,21\) The predominant aberrations are loss of whole chromosomes 7 and 5 or various parts of the long arms of these two chromosomes. In addition, nonrandom abnormalities have been reported, particularly of chromosomes 17 and 21.

It is possible that the generally short survival of patients is the reason for the as yet sparse discussion of prognostic factors in t-MDS and t-ANLL. However, the combined fact that some patients with t-MDS may survive for prolonged periods of time,\(^15,16\) that others with overt t-ANLL may respond to intensive chemotherapy as do patients with de novo leukemia,\(^15,24,22\) and may become long-term survivors, and that bone marrow transplantation is now in widespread clinical use, makes re-evaluating prognostic factors in t-MDS and t-ANLL an urgent issue.

Whereas the presence of characteristic chromosome aberrations has been shown to be of major importance in the diagnosis of t-MDS,\(^7,8,11,15\) their role as a prognostic factor has so far remained controversial. We have previously presented data suggesting that the number of chromosome aberrations in t-MDS and t-ANLL is a prognostic factor,\(^15,19\) as in some studies of the de novo myelodysplastic syndromes.\(^26-29\) However, another major study has not confirmed our findings,\(^17\) and in de novo myelodysplasia and acute nonlymphocytic leukemia, it is the specific chromosome aberrations rather than their number that have been proposed as an important prognostic factor.\(^20-23\)

This study extends our experience to 91 consecutive cases of t-MDS and t-ANLL examined cytogenetically. It was undertaken to re-evaluate the frequency of specific chromosome abnormalities, to evaluate whether they are consistently present in all abnormal mitoses at diagnosis or only in a subclone in the individual patient, to study cytogenetic evolution during the course of the disease, and to search for a possible relationship between specific chromosome aberrations and important clinical and pathologic parameters. Finally, a Cox regression analysis was carried out to examine the importance of cytogenetic parameters as compared with major clinical and pathologic findings as independent prognostic factors in patients with t-MDS and t-ANLL.

PATIENTS AND METHODS

Patient characteristics and cytologic classification. During the period between 1987 and 1989, 21 new cases of t-MDS or t-ANLL were diagnosed at our institution in patients previously treated with radiotherapy and/or chemotherapy (Table 1). Seven patients had previously received treatment for malignant lymphomas; six, for breast cancer; seven, for various other malignancies; and one patient had received treatment with azathioprine for sarcoidosis. The 21 new cases of t-MDS or t-ANLL, together with the 70 cases for which clinical and complete cytogenetic data have been reported previously,\(^9,13,15,19,26\) comprise our total experience for the period between 1976 and 1989. Overt t-ANLL was classified according to...
Table 1. Clinical Characteristics, Bone Marrow Cytology, and Cytogenetic Findings at Diagnosis in a New Series of Patients With t-MDS or t-ANLL

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Primary Tumor Histology/ Stage</th>
<th>Type of Treatment for Primary Tumor (no., duration)</th>
<th>Status of Primary Tumor (no. of MDS or ANLL (no. of AN)</th>
<th>Survival Time of MDS or ANLL (no. of AN)</th>
<th>Duration of MDS or ANLL (no. of AN)</th>
<th>FAB Type of Malignant Leukemia</th>
<th>Karyotype of BM, Mitoses (abnormal/normal)</th>
<th>Antileuk. Chemother. (type, response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>76/M</td>
<td>Hodgkin NS/IIA</td>
<td>Me + VCR + Pred + Pro (16)</td>
<td>CR (3)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>46,XY, 6, 6, 15, 16, 17, +der(6)(q23); 7, +der(6)(q23); +der(11)(q15.18); (12)q12:12; (17)q12:17 = 13; 45,x, stemline with 18,del(16) and (12) without 18; +del(18)=7/45, as stemline with (18)=5</td>
<td>—</td>
</tr>
<tr>
<td>90</td>
<td>43/F</td>
<td>Hodgkin NS/V/IIA</td>
<td>CCNU + Vlb + Pro + Pred (8)</td>
<td>PR (3)</td>
<td>36± 36± 36±</td>
<td>46,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>Acl + AraC/CR 12 mo</td>
<td>HD AraC/CR 12 mo</td>
</tr>
<tr>
<td>91</td>
<td>67/F</td>
<td>Non-Hodgkin NM/I/A</td>
<td>Ctx (38)</td>
<td>CR (3)</td>
<td>36± 36± 36±</td>
<td>46,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>92</td>
<td>60/F</td>
<td>Non-Hodgkin DWML/IIA</td>
<td>VCR + Pred + Sm (2)</td>
<td>PR (3)</td>
<td>36± 36± 36±</td>
<td>46,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>93</td>
<td>49/M</td>
<td>Non-Hodgkin NPDL/I/A</td>
<td>VCR + Pred + Sm (2)</td>
<td>PR (3)</td>
<td>36± 36± 36±</td>
<td>46,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>94</td>
<td>72/M</td>
<td>Non-Hodgkin NM/I/A</td>
<td>X-ray rhinopharynx and neck, 36 Gy</td>
<td>CR (3)</td>
<td>36± 36± 36±</td>
<td>46,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>95</td>
<td>65/M</td>
<td>Non-Hodgkin lymphoblast/E</td>
<td>CHOP (5)</td>
<td>CR (3)</td>
<td>36± 36± 36±</td>
<td>46,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>96</td>
<td>74/F</td>
<td>Multiple myeloma</td>
<td>Maiphalan + Pred (12)</td>
<td>PR (3)</td>
<td>36± 36± 36±</td>
<td>46,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>97</td>
<td>63/F</td>
<td>Breast cancer duct care/ disseasement</td>
<td>X-rays Mc Whirter, 40.7 Gy</td>
<td>Ctx (15)</td>
<td>112</td>
<td>45,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>98</td>
<td>61/F</td>
<td>Breast cancer duct care/ disseasement</td>
<td>X-rays Mc Whirter, 40.7 Gy</td>
<td>X-rays Mc Whirter, 64 Gy</td>
<td>Ctx + SFU + Mtx + Mtx (22)</td>
<td>112</td>
<td>45,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
</tr>
<tr>
<td>99</td>
<td>56/F</td>
<td>Breast cancer duct care/ disseasement</td>
<td>X-rays Mc Whirter, 32. Gy</td>
<td>X-rays Mc Whirter, 45. Gy</td>
<td>+ Ctx + SFU + Mtx + Mit + Mit + Tam (22)</td>
<td>112</td>
<td>45,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
</tr>
<tr>
<td>100</td>
<td>67/F</td>
<td>Breast cancer duct care/ disseasement</td>
<td>X-rays Mc Whirter, 50 Gy</td>
<td>Ctx + SFU + Mtx + Mtx + Mtx (22)</td>
<td>112</td>
<td>45,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>101</td>
<td>42/M</td>
<td>Breast cancer duct care/ disseasement</td>
<td>X-rays Mc Whirter, 50 Gy</td>
<td>Ctx + SFU + Mtx + Mtx (22)</td>
<td>112</td>
<td>45,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>102</td>
<td>39/F</td>
<td>Breast cancer duct care/ disseasement</td>
<td>X-rays me, 12.5 Gy</td>
<td>X-rays me, 12.5 Gy</td>
<td>X-rays me, 12.5 Gy</td>
<td>112</td>
<td>45,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
</tr>
<tr>
<td>103</td>
<td>54/F</td>
<td>Small-cell lung cancer/ extensive</td>
<td>X-rays + CCNU + VCR + VP16 (11)</td>
<td>X-rays me, 12.5 Gy</td>
<td>X-rays me, 12.5 Gy</td>
<td>112</td>
<td>45,XX, 7± 7± 7± (q27p)</td>
<td>29/0</td>
<td>—</td>
</tr>
</tbody>
</table>

(Continued on following page)
the FAB recommendations,17 and t-MDS was classified as previously described.9,11,19 no distinction now being made between preleukemia and the acute myeloproliferative syndrome.

Cytogenetic studies. Cytogenetic investigations were carried out using GTL banding technique after a 1- to 2-day culture of a bone marrow sample. Results were expressed in accordance with the International System for Human Cytogenetic Nomenclature (ISCN).38 Furthermore, patients were classified as NN, AN, or AA based on the presence of normal mitoses only, a mixture of normal and abnormal mitoses, or abnormal mitoses only, as previously reported for de novo ANLL.39 The number of chromosome aberrations was estimated, assessing a translocation between two chromosomes or abnormal mitoses, or abnormal mitoses only, as previously described.9,20,21 no distinction now being made between preleukemia and the acute myeloproliferative syndrome.

Survival was calculated from the first diagnosis of t-MDS or t-ANLL between groups of patients were compared using the Cox proportional hazards model41 using the BMDP program42 All recorded factors (Table 2) were included in the multivariate analysis initially, and a step-down procedure was adopted by removal of the least significant factor and repetition of the analysis until only those factors that had significant prognostic influence (P < .05) were retained. For each factor, a regression coefficient was estimated as previously reported.4 The statistical significance of differences in frequencies between groups of patients was assessed with Fisher’s exact test (two-sided), and differences in the latent period for development of t-MDS or t-ANLL between groups of patients were evaluated by Wilcoxon’s two-sample test (two-sided).

RESULTS

Clinical data and results of cytogenetic investigation of the bone marrow of 21 new cases of t-MDS and t-ANLL are shown in Table 1. Six patients showed loss of whole chromosome 7, one patient loss of chromosome 5, five patients loss of various parts of the long arm of chromosome 7, and two patients loss of parts of the long arm of chromosome 5. Rearrangement of band 11q23 was observed in five patients. Two of our new patients with t-MDS showed deletions of 13q, including band 13q14, as the only abnormality, and two patients showed a t(8;21)(q22;q22), one of these as part of a complex karyotype also including a del(7)(q32).

Table 1. Clinical Characteristics, Bone Marrow Cytology, and Cytogenetic Findings at Diagnosis in a New Series of Patients With t-MDS or t-ANLL (Cont’d)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Primary Tumor Type</th>
<th>Treatment of Primary Tumor (Duration)</th>
<th>Status of Primary Tumor</th>
<th>Time to Development of MDS or ANLL (moa)</th>
<th>Survival From MDS or ANLL (moa)</th>
<th>FAB Type</th>
<th>Overt Leukemia</th>
<th>Karyotype of BMc</th>
<th>Mitoses (abnormal/normal)</th>
<th>Antileuk. Chemother. Type</th>
<th>Antileuk. Chemother. Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>Thymoma</td>
<td>Ctx + CCNU + VCR + Pred (18)</td>
<td>CR</td>
<td>94</td>
<td>3</td>
<td>4</td>
<td>M1</td>
<td>47; X0, -7, +8, +t(1q7p)</td>
<td>32/0</td>
<td>Ad + AraC/ NR</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>Testicular cancer</td>
<td>Cis-pl + Bleo + VP16 + VCR (8)</td>
<td>CR</td>
<td>62</td>
<td>6</td>
<td>M4</td>
<td>46; XY</td>
<td>0/14</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>Testicular cancer</td>
<td>X-rays paraacetic + pelvic fields, 40.4 Gy</td>
<td>CR</td>
<td>90</td>
<td>2</td>
<td>M2</td>
<td>46; XV; t(8;21)</td>
<td>(2p22;22q23)</td>
<td>26/26</td>
<td>Ad + AraC/ NR</td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>Laryngeal cancer</td>
<td>X-rays neck, 63 Gy</td>
<td>CR</td>
<td>161</td>
<td>1</td>
<td>M5a</td>
<td>47; XY, -11, +19, +del(11)</td>
<td>(11;17)(q23;q23) or 24;7</td>
<td>22/4</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>Urinary bladder cancer</td>
<td>X-rays urinary bladder, 40 Gy</td>
<td>PD</td>
<td>29</td>
<td>2</td>
<td>2</td>
<td>45; X0, -3, -7, -16, +del(12)(p11)</td>
<td>-2mar</td>
<td>20/2</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMC, bone marrow cells; NS, nodular sclerosis; NM, nodular mixed; DWDL, diffuse well-differentiated lymphocytic; NPD1, nodular poorly differentiated lymphocytic; Ma, medulloblastoma; VCR, vincristine; Pred, prednisone; Pro, procarbazine; Str, streptogin; Ctx, cyclophosphamide; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; Cbl, chlorambucil; Adm, adriamycin; 5FU, 5-fluorouracil; Cis-pl, cisplatin; HMM, hexamethylmelamine; Mtx, methotrexate; Mit, mitoxantrone; Tam, tamoxifen; CCNU, lomustine; Bleo, bleomycin; Vlb, vincristine; VP16, etoposide; Aza, azathioprine; Ara-C, cytosine arabinoside; AMSA, amasan; VAMP, vincristine + 6-mercaptopurin + methotrexate + prednisone; Epi, 4-epidoxorubicin; HD, high dose; CR, complete remission; PR, partial remission; PD, progressive disease; NR, no response; DNR, daunorubicin.

Follow-up procedure and treatment. All patients were followed closely till death or termination of this study in July 1989. In patients with t-MDS, supportive therapy was given when required with erythrocyte and platelet transfusions. Infections were treated with antibiotics, and in a few cases, nonintensive chemotherapy with regimens such as low-dose cytosine arabinoside was attempted without obtaining any improvement. Overt t-ANLL was treated with daunorubicin for 3 days plus cytosine arabinoside as continuous intravenous infusion for 7 days, as previously described.9,15 in some recent cases, daunorubicin was replaced by aclacinomycin in an equivalent dose. In patients obtaining a complete remission, an intensification program composed of alternating courses of daunorubicin, cytosine arabinoside, amasanine, and etoposide was administered for a period of 6 months.
Table 2. Cox Regression Analysis of Prognostic Factors for 91 Cases of t-MDS and t-ANLL

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>-0.003</td>
<td>0.011</td>
<td>0.81</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>-0.368</td>
<td>0.262</td>
<td>0.16</td>
</tr>
<tr>
<td>Primary malignancy (lymphoma/others)</td>
<td>0.628</td>
<td>0.239</td>
<td>0.008</td>
</tr>
<tr>
<td>Primary malignancy (CR Y/N)</td>
<td>0.696</td>
<td>0.257</td>
<td>0.008</td>
</tr>
<tr>
<td>Previously treated with alkylating agents (Y/N)</td>
<td>-0.413</td>
<td>0.358</td>
<td>0.24</td>
</tr>
<tr>
<td>Myelodysplasia observed (Y/N)</td>
<td>-0.084</td>
<td>0.381</td>
<td>0.83</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>-0.016</td>
<td>0.009</td>
<td>0.07</td>
</tr>
<tr>
<td>Granulocytes (x 10^9/L)</td>
<td>0.001</td>
<td>0.003</td>
<td>0.78</td>
</tr>
<tr>
<td>Thrombocytes (x 10^9/L)</td>
<td>-0.007</td>
<td>0.003</td>
<td>0.013</td>
</tr>
<tr>
<td>Marrow cellularity increased (Y/N)</td>
<td>0.245</td>
<td>0.167</td>
<td>0.15</td>
</tr>
<tr>
<td>Marrow blasts + promyelocytes (%)</td>
<td>0.002</td>
<td>0.012</td>
<td>0.87</td>
</tr>
<tr>
<td>Cytogenetics (NN/AN/AA)</td>
<td>0.124</td>
<td>0.200</td>
<td>0.54</td>
</tr>
<tr>
<td>Chromosome 5 and/or 7 abnormal (Y/N)</td>
<td>0.363</td>
<td>0.298</td>
<td>0.23</td>
</tr>
<tr>
<td>Cytogenetics (no. of aberrations)</td>
<td>0.057</td>
<td>0.032</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values in parenthesis represent estimates based exclusively on patients with MDS (n = 62).

Loss of a whole chromosome 7 was the most frequently observed abnormality present in 32 patients (Figs 1 and 2), in 30 as a consistently present aberration seen in all abnormal mitoses studied. In addition, six patients had lost the whole long arm of a chromosome 7 as a result of an unbalanced translocation, and 10 showed unbalanced translocations or apparently terminal deletions with loss of various parts of the long arm of a chromosome 7. Break point for the deletions was most often 7q22; the critical region always deleted comprising bands 7q32 to 7qter. In 15 of the 16 patients, the defects of 7q were consistently present aberrations.

Six patients had lost a whole chromosome 5 and three patients the whole long arm of a chromosome 5 as a result of an unbalanced translocation (Fig 1). Twelve patients showed interstitial deletion of various parts of the long arm of a chromosome 5. The proximal break point varied between bands 5q13 and 5q22 and the distal break point between bands 5q31 and 5q35, indicating a critical region from 5q22 to 5q31. All the abnormalities of chromosome 5 were consistently present.

Nine patients showed rearrangements of band 11q23, including the classic t(9;11)(p21;q23) in four cases (Figs 1 and 2). Five patients with 11q23 rearrangement belong to our new series of cases, whereas data for four patients have been presented previously. Among these, cases 66 and 76 were originally considered as having a normal karyotype. However, a reexamination of new preparations showed a t(9;11)(p21;q23) in all 41 mitoses in case 66 and in all 24 mitoses in case 76. In seven of the patients, the 11q23...

Fig 1. Chromosome aberrations consistently present in all abnormal mitoses at diagnosis of t-MDS or t-ANLL in 91 consecutive patients. Thirteen cases presented a normal karyotype. Each box represents one case: ■, gain; □, loss; ×, balanced translocation; ■, unbalanced translocation or deletion.

Fig 2. Chromosome aberrations inconsistently present in one or several but not all abnormal clones at diagnosis of t-MDS or t-ANLL (18 patients) and evolutionary chromosome aberrations observed during the course of the disease (12 patients). Black or white circles indicate evolutionary aberrations; other symbols defined in legend to Fig 1.
rearrangement was observed as the only abnormality present, and in eight cases, it was a consistently present aberration. Other consistently present aberrations (Fig 1) include monosomy of chromosomes 17 and 18, trisomy 1q, rearrangements of 3q, 17p aberrations, and rearrangements of 21q with breakpoint at band 21q22. Generally, loss of whole chromosomes predominated as consistently present aberrations over gain of whole chromosomes (Fig 1).

Inconsistently present aberrations at diagnosis as shown in Fig 2 differed markedly from consistently present aberrations (Fig 1). As far as numerical aberrations are concerned, gain of whole chromosomes predominated over loss. Four patients presented trisomy 8, and only two patients had lost a whole chromosome 7. Among structural abnormalities, three patients showed rearrangement with loss of the short arm of chromosome 7 and three trisomy for the long arm of chromosome 21. Only one patient showed rearrangement with loss of a part of the long arm of chromosome 7. Monosomy of chromosome 5 or loss of parts of the long arm were never observed as inconsistently present aberrations. Evolutionary aberrations during the course of the disease were observed in 12 patients (Fig 2) of 46 reexamined during the course of the disease. Time from diagnosis to reexamination varied between 3 weeks and 5 years, according to the clinical course of the disease. Like the inconsistently present aberrations, the evolutionary aberrations differed markedly from the consistently present aberrations. Abnormalities of chromosome 5 were not observed as evolutionary events. Only one patient with overt leukemia, who initially presented a normal karyotype and obtained a complete remission after daunorubicin and cytosine arabinoside at relapse, presented a characteristic unbalanced translocation: −7;+t(1q;7p) with loss of the long arm of a chromosome 7.

In our total series of 91 patients, 40 patients had previously been treated for malignant lymphomas, five patients for other hematologic malignancies, 45 patients for a solid tumor, and one patient for a benign disease. At the diagnosis of t-MDS or t-ANLL, the primary disease was in complete remission in 57 patients, whereas 34 had an active primary tumor, in many cases in an advanced stage with bone marrow involvement. Eleven patients had previously been treated with alkylating agents alone, and 63 patients had been receiving alkylating agents plus other types of therapy, including radiotherapy in 33 patients. Ten patients had received radiotherapy alone, three patients radiotherapy plus chemotherapy not including alkylating agents, and four patients chemotherapy alone without alkylating agents.

At diagnosis, 62 patients presented with MDS, whereas 29 patients had overt leukemia of the FAB subtypes shown in Table 3. The bone marrow cellularity was increased in 68 patients, including the 29 patients with overt leukemia. Eight patients with MDS had a normal cellularity and 15 with MDS, a decreased cellularity. During follow-up, 26 patients with t-MDS developed overt leukemia (Table 3). Close correlations were observed between previous treatment with alkylating agents and the presence of a myelodysplastic phase (P = .00007, Table 4), between previous treatment with alkylating agents and chromosome 5 and/or chromo-

some 7 abnormalities (P = .00007, Table 4), and between the presence of a myelodysplastic phase and chromosome 5 and/or chromosome 7 abnormalities (P = .000001, Table 4).

The latent period for development of leukemia for the nine patients with involvement of 11q23 was often short (median, 24 months), as compared with 49 months for 73 patients without abnormalities of chromosome 11. Evaluated by Wilcoxon’s two-sample test (two-sided), the differences in latent periods between the two groups of patients are significant (P = .04). Seven of nine cases with rearrangement of 11q23 presented with overt leukemia, and seven of eight overt leukemias were of FAB subtypes M4 or M5a.

Results of a Cox regression analysis of prognostic factors for survival from diagnosis of t-MDS or t-ANLL for all 91 patients are shown in Table 2. Clinical findings, basic laboratory results, and results of bone marrow cytology and cytogenetic studies are included in the model. The two most important and independent factors indicating a favorable prognosis were complete remission of the primary malignancy and a malignant lymphoma as primary tumor (P = .008). Apart from these, only the thrombocyte count at diagnosis was an independent prognostic factor (P = .013). When evaluated separately for 62 patients with MDS, the hemoglobin concentration, the percentage of blasts and promyelocytes in the bone marrow, and the number of chromosome aberrations were other independent and significant prognostic factors (P = .004, P = .046, and P = .048 respectively). No other factor approached significance.
The importance of the prognostic factors for prediction of
survival in patients with t-MDS or t-ANLL is shown in Fig 3.
The observed survival is presented as a Kaplan-Meier esti-
mate together with the predicted most favorable and most
unfavorable prognosis, taking into consideration the three
prognostic factors: remission status of the primary tumor,
previous malignant lymphoma or other disease, and the
thrombocyte count at diagnosis (in our study, varying be-
tween 250 x 10^9/L and 5 x 10^9/L). Considerable variation
is observed, for instance, in the predicted median survival
(2.8 to 37 months).

After overt t-ANLL had developed, intensive antileuke-
emic chemotherapy was attempted in 36 patients. Seventeen
of these obtained a complete remission (Table 5). The
strongest predictive factor for a favorable response was
absence of a myelodysplastic phase of the disease
(P = .0014).

DISCUSSION

The present study emphasizes that in most cases of t-MDS
or t-ANLL, the bone marrow cells show characteristic clonal
cytogenetic abnormalities, predominantly loss of whole chro-
mosomes 5 or 7 or various parts of the long arms of these two
chromosomes. Using a new simple classification of clonal
chromosome aberrations as consistently or inconsistently
present at diagnosis, and comparing the results obtained with
the cytogenetic evolution during the course of the disease
(Figs 1 and 2), an abnormal chromosome 5 was always
consistently present at diagnosis, as were the chromosome 7
abnormalities in most of the patients. Together with the
recent mapping of several genes for important hematopoietic
growth factors and growth factor receptors to the critical
deleted bands on the long arm of chromosome 5.45-47 These
findings suggest that at least the chromosome 5 defects are
directly involved in the pathogenesis of MDS and ANLL. In
addition, as previously discussed, cytogenetic abnormalities
primarily of chromosomes 5 and 7 are of essential diagnostic
importance, particularly in the early stages of t-MDS with a
hypoplastic bone marrow and without increased percentage
of blasts.78,15,19 Of 62 patients with t-MDS in our study, 15
belong to this category (Table 3).

The marked general difference between all consistently
present aberrations and the inconsistent or evolutionary
aberrations, as evident by comparing Figs 1 and 2, supports
our distinction between the two types of chromosome abnor-
mality and our suggestion that the consistently present
aberrations most often represent primary cytogenetic events
during leukemogenesis.

Other previously described characteristic aberrations, such
as loss of a whole chromosome 17 or 18 and rearrangements
of the short arm of chromosome 17 and the long arm of
chromosome 21 at band 21q22, were also most often demon-
strated to be consistently present aberrations (Fig 1). In
addition, the present study confirmed 11q23 rearrangements
as a new nonrandom cytogenetic abnormality of t-ANLL,
first reported recently.46-50 It is striking that in eight of nine
patients this abnormality was observed as a consistently
present aberration and only as inconsistently present in one
patient, who also presented a deletion of the long arm of
chromosome 7. Furthermore, the 11q23 rearrangement was
the only abnormality present in seven of the nine patients.
Equally surprising was the short latent period for develop-
ment of t-ANLL often observed in these patients, and the
fact that seven of the nine patients presented in overt
leukemia without a myelodysplastic phase. As previously
discussed,47 all these facts suggest a different pathogenetic
mechanism for development of t-ANLL with 11q23 rear-
rangements as compared with cases with defects of chro-
mosomes 5 and 7. Two new cases of t-MDS, both with a short
survival, presented deletions of the long arm of a chromo-
some 13, including band 13q14. The deletions occurred alone
as consistently present aberrations in both cases. Deletions
including 13q14 have previously been observed in patients
with myeloid disorders, for instance de novo myelodysplasia,51
and 13q14 carries the recessive gene of putative importance
in retinoblastoma.

In patients previously treated with alkylating agents,
almost all observed cases of t-MDS and t-ANLL must be
considered as directly induced by therapy. For example in
Hodgkin's disease, relative risks (ratio of observed:expected
cases) of 117 to 133 have been observed.22 This indicates that
statistically, only one case in 117 to 133 cases of t-ANLL
related to treatment with alkylating agents can be expected
to arise de novo. This high specificity is interesting in relation
to our finding of close correlations between previous therapy
with alkylating agents, the presence of a myelodysplastic
phase, and abnormalities of chromosome 5 or 7 (Table 4).
Only a minor group of patients with de novo ANLL share the
same characteristics.30-35 By comparison, in patients previ-
PROGNOSTIC FACTORS IN THERAPY-RELATED LEUKEMIA

Table 5. Response of Overt t-ANLL to Intensive Chemotherapy

<table>
<thead>
<tr>
<th>Cytogenetic Characteristics (CR/no. patients treated)</th>
<th>Chromosome 5 or 7 Abnormalities</th>
<th>Other Abnormalities Only</th>
<th>Normal Karyotype</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic phase observed</td>
<td>1/12</td>
<td>0/1</td>
<td>1/2</td>
<td>2/15</td>
</tr>
<tr>
<td>Myelodysplastic phase not observed</td>
<td>3/3</td>
<td>5/10</td>
<td>7/8</td>
<td>16/21</td>
</tr>
<tr>
<td>Total</td>
<td>4/15</td>
<td>5/11</td>
<td>8/10</td>
<td>17/36</td>
</tr>
</tbody>
</table>

*Fisher's exact test, two-sided.

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