Clonal Karyotypic Hematopoietic Cell Abnormalities Occurring After Autologous Bone Marrow Transplantation for Hodgkin’s Disease and Non-Hodgkin’s Lymphoma

By S. Thomas Traweek, Marilyn L. Slovak, AuayPorn P. Nademanee, Russell K. Brynes, Joyce C. Niland, and Stephen J. Forman

Over a 6-year period, 275 patients were treated with autologous bone marrow transplantation (auto-BMT) for advanced-stage malignant lymphoma. After BMT, clonal chromosomal abnormalities were detected in hematopoietic cells from 10 patients. All 10 had genetically normal BMs at the time of stem cell harvest. The cytogenetic changes were first detected 1.8 to 6.5 years (mean, 3.9) after induction chemotherapy, and 0.5 to 3.1 years (mean, 1.4) after transplantation, and were characteristic of those reported for therapy-related myelodysplastic syndromes (MDS) in 9 of the patients: abnormalities of chromosomes 5 or 7 (classical-form) were present in 4, 11q23 or 21q22 abnormalities (topoisomerase II-related form) were detected in 3, and a combination of both forms was seen in 2 patients. Clonal 2p abnormalities were found in the 1 remaining patient. The abnormal karyotypes were associated with morphologically recognizable MDS in 3 patients and with acute myeloid leukemia (AML) arising in MDS in 2. Four of these patients have died: 3 of AML and 1 of infection. One patient is still alive with cytopenia. The clonal cytogenetic abnormalities were not associated with MDS in 5 patients: 1 has died of recurrent lymphoma, 2 have cytopenia, and 2 still have no morphologic or clinical evidence of MDS after short follow-up (4 and 13 months). Compared with a control group matched for disease, length of follow-up, and treatment with autologous BMT, there were no statistically significant associations between the development of clonal chromosomal abnormalities and age, number of chemotherapeutic regimens, prior local radiation, BMT conditioning regimen (with or without total body irradiation), or type of lymphoma. These studies show that the risk of developing clonal cytogenetic changes after autologous BMT for malignant lymphoma is approximately 9% at 3 years, even when pre-BMT karyotypic studies are normal. The exact significance of these cytogenetic abnormalities in the absence of MDS or AML is unclear.

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Autologous bone marrow transplantation (auto-BMT) is being used with increasing frequency in the treatment of human leukemias, lymphomas, and solid tumors. Also known as autologous stem cell rescue or support, auto-BMT functions primarily to allow dose escalation of chemotherapy and radiation, and is used most often in patients who have failed initial induction and salvage therapeutic regimens. Therefore, patients with Hodgkin’s disease (HD) or non-Hodgkin’s lymphoma (NHL) treated with auto-BMT usually have been treated on multiple occasions before the time of BM harvest, and any permanent insult sustained by the normal hematopoietic stem cells as a consequence of the previous therapy could potentially result in alterations of post-BMT hematopoiesis, such as myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML).

In a previous report, we suggested that cytogenetic studies at the time of BM harvest could be used to detect marrow cells that had been previously damaged by extensive treatment. Since the time of that study, karyotypic analyses have been performed on all patients considered for autologous stem cell rescue at the City of Hope National Medical Center (Duarte, CA), and clonal cytogenetic changes typical of therapy-induced disease have been considered a finding of sufficient significance to preclude use of autologous cells for BMT.

This report describes a group of patients who proceeded to auto-BMT for either HD or NHL and subsequently developed karyotypic changes typical of MDS despite having normal cytogenetic studies before transplantation. The clinical and pathologic features of these patients are discussed, and the risk factors and significance of clonal cytogenetic abnormalities after auto-BMT are analyzed.

Materials and Methods

Over a 6-year period (July 1987 through July 1993), 275 patients with advanced-stage malignant lymphoma underwent auto-BMT at the City of Hope National Medical Center. Informed consent was obtained from each patient in accordance with institutional guidelines, and all patients were treated on protocols approved by the City of Hope Medical Center Institutional Review Board. The technique of BM harvest and cryopreservation have been previously described. Bilateral posterior iliac crest biopsies were performed to exclude involvement by lymphoma before harvest, and no purging of the marrow was performed before reinfusion. Some of the patients received a combination of BM and peripheral blood stem cells (PBSCs), collected via leukopheresis. Patients with previously documented BM involvement by lymphoma were treated using only PBSCs. Three different BMT preparative regimens were used during this time period. Patients who had not been previously treated with radiation therapy received either 500 to 750 cGy total body irradiation (TBI) or 1,200 cGy fractionated TBI (FTBI) in combination with 60 mg/kg etoposide (VP-16) and 100 mg/kg cyclophosphamide.

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The patients previously treated with local radiotherapy received 450 mg/m^2 carmustine (BCNU) instead of TBI or FTBI. Those with residual bulky lymphoma masses received an involved-field radiation boost of 2,000 cGy during the 2 weeks before transplantation.

Of the 275 patients treated with auto-BMT for lymphoma, 10 had normal cytogenetic studies on BM samples immediately before transplantation, and subsequently developed clonal karyotypic abnormalities after BMT; these patients form the basis of this report. A summary of the pertinent patient data for this group is given in Table 1. The primary diagnosis, either HD or NHL, was confirmed by review of the relevant biopsy material at this institution. Cytogenetic studies were performed according to standard methods, and the karyotypes were described according to the recommendations of ISCN (1991). Patient follow-up information was derived from the patients' charts and from the hematology staff. Pathologic examination of the BM samples taken before and after transplantation was performed by two hematopathologists without knowledge of the associated clinical or cytogenetic findings. French-American-British (FAB) criteria were applied in the diagnosis of AML. A morphologic diagnosis of MDS was made also according to FAB criteria, with some modification. Specifically, because mild hematopoietic cell atypia is common after chemotherapy and BMT, being especially evident in erythroid precursors, the unequivocal presence of dysplastic features in all three hematopoietic cell lines was required for a definitive diagnosis of MDS. The first patient in this series has been previously reported.

### Table 1. Patient Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>DX</th>
<th>No. of Treatment Regimens*</th>
<th>Type of Treatment Regimens</th>
<th>Status at BM</th>
<th>BM Conditioning Regimen</th>
<th>Source of Stem Cells</th>
<th>Chemo Rx to MDS (yrs)</th>
<th>BM to MDS (yrs)</th>
<th>Current Status/ Survival</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>43/F</td>
<td>HD</td>
<td>3†</td>
<td>MOPP-ABV VP-16/CCNU</td>
<td>2 rel</td>
<td>TBI/VP-16/Cy</td>
<td>PB/BM</td>
<td>6.5</td>
<td>0.9</td>
<td>Died of AML</td>
</tr>
<tr>
<td>2</td>
<td>20/M</td>
<td>B-DLC</td>
<td>1</td>
<td>MACOP-B</td>
<td>1 CR</td>
<td>FTBI/VP-16/Cy</td>
<td>PB</td>
<td>3.5</td>
<td>3.1</td>
<td>Cytopenic</td>
</tr>
<tr>
<td>3</td>
<td>30/F</td>
<td>HD</td>
<td>2†</td>
<td>MOPP-ABV-VE</td>
<td>2 CR</td>
<td>BCNU/VP-16/Cy</td>
<td>BM</td>
<td>4.3</td>
<td>2.4</td>
<td>Died of infection</td>
</tr>
<tr>
<td>4</td>
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<td>SNC</td>
<td>2</td>
<td>MACOP-B</td>
<td>1 CR</td>
<td>FTBI/VP-16/Cy</td>
<td>PB</td>
<td>2.1</td>
<td>1.8</td>
<td>Died of AML</td>
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<tr>
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<td>2</td>
<td>MOPP-ABV-AC</td>
<td>2 CR</td>
<td>FTBI/VP-16/Cy</td>
<td>PB/BM</td>
<td>1.8</td>
<td>0.8</td>
<td>MDS†</td>
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<tr>
<td>6</td>
<td>22/M</td>
<td>T-DLC</td>
<td>2</td>
<td>M-BACOD</td>
<td>2 CR</td>
<td>FTBI/VP-16/Cy</td>
<td>PB</td>
<td>2.3</td>
<td>1.0</td>
<td>NED, 13 mo</td>
</tr>
<tr>
<td>7</td>
<td>42/M</td>
<td>FSC</td>
<td>3</td>
<td>M-BACOD</td>
<td>1 rel</td>
<td>FTBI/VP-16/Cy</td>
<td>PB</td>
<td>4.2</td>
<td>2.0</td>
<td>Cytopenic</td>
</tr>
<tr>
<td>8</td>
<td>38/M</td>
<td>B-IBL</td>
<td>3†</td>
<td>MOPPABV BCVPP CEF</td>
<td>4 CR</td>
<td>BCNU/VP-16/Cy</td>
<td>PB</td>
<td>5.8</td>
<td>0.5</td>
<td>Died of NHL</td>
</tr>
<tr>
<td>9</td>
<td>27/F</td>
<td>FSC</td>
<td>3†</td>
<td>MACOP-B</td>
<td>3 CR</td>
<td>BCNU/VP-16/Cy</td>
<td>PB</td>
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<td>1.7</td>
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<td>HD</td>
<td>3†</td>
<td>MOPP-ABV-ESAP</td>
<td>3 rel</td>
<td>BCNU/VP-16/Cy</td>
<td>BM</td>
<td>2.2</td>
<td>0.7</td>
<td>Died of AML</td>
</tr>
</tbody>
</table>

Abbreviations: B-DLC, diffuse large cell lymphoma; B-cell type; SNC, small non-cleaved cell lymphoma; T-DLC, large cell lymphoma; T-cell type; FCS, follicular small cleaved cell lymphoma; B-IBL, immunoblastic lymphoma, B-cell type; NED, no evidence of hematologic disease, the time of follow-up is also given; Cy, cyclophosphamide.

* No. of treatment regimens represents the number of different multicycle, multiagent chemotherapeutic combinations used as treatment before BMT.
† Also received local radiation.
‡ Patient no. 5 also has recurrent HD.
§ Patient no. 9 has recurrent NHL.

Statistical analysis. For each patient that developed hematopoietic cell chromosomal abnormalities, three control patients were chosen, matched for disease (HD or NHL) and length of follow-up from original diagnosis (±3 months). All control patients had also undergone high-dose chemotherapy followed by autologous hematopoietic cell rescue. Conditional logistical regression was performed using these case-control sets to determine whether the following were significant risk factors for the development of clonal karyotypic changes: diagnosis, age at transplantation, source of stem cell (PB or BM and PB), previous radiation therapy, number of chemotherapy regimens, and type of BMT conditioning (with or without TBI). The probability of developing abnormal chromosomes was estimated by the method of Kaplan and Meier and compared using the log rank test statistic.

RESULTS

In the patient population treated with auto-BMT for malignant lymphoma, the primary diagnosis was HD in 108 (39%)
CHROMOSOMATIC ABNORMALITIES AFTER AUTO-BMT

Fig. 1. GTG-banded karyotype of sideline 2 (sdl 2) from patient no. 3. The karyotype designation is 44,XX,5; dic(6q;21q); del(6q)(q23q25), -9, -13, +mar1, +mar2. The arrows show clonal aberrations. Monosomy 5, a classic therapy-related chromosomal anomaly, was observed as the sole abnormality in the stemline. Abnormalities of chromosome band 21q22, seen in this karyotype as part of a dicentric chromosome, have been associated with exposure to topoisomerase II inhibitors such as VP-16.

and NHL in 167 (61%). Ten patients from this group developed clonal karyotypic abnormalities after BMT. Cytogenetic studies performed before BMT on these 10 patients were normal. As shown in Table 1, 4 of these patients underwent BMT for HD and 6 were treated for a variety of NHLs.

All patients were treated with chemotherapy for their disease before BMT, and some were treated repeatedly. Specifically, 5 (50%) of the patients were subjected to three different chemotherapeutic regimens as a consequence of multiple disease relapses. Half of the patients also received local radiation therapy in addition to multagent chemotherapy before BMT. At the time of BMT, 3 patients were in relapse and 7 were in clinical and radiologic remission. The time interval from diagnosis to BMT varied from 0.5 to 5.8 years (mean, 2.7). The pre-BMT features of these patients are summarized in Table 1. Two patients with NHL and 1 with HD have recurred after transplantation; 1 of these patients has died of lymphoma.

None of the patients in this study had clinical, morphologic, or cytogenetic evidence of a hematologic abnormality before BMT. However, all 10 developed BM chromosomal abnormalities after BMT, occurring from 1.8 to 6.5 years (mean, 3.9) after induction chemotherapy, and from 0.5 to 3.1 years (mean, 1.4) after transplantation. The cytogenetic changes were characteristic of those reported for therapy-related MDS in 9 patients. Specifically, abnormalities of chromosome 5 or 7 (classical form of chromosomal MDS changes) were present in 4 cases, 11q23 or 21q22 abnormalities (topoisomerase II-related form) were detected in 3 cases, and a combination of both forms was seen in 2 patients (Fig 1). Clonal 2p abnormalities were present in the remaining patient. The initially abnormal cytogenetic findings for all 10 patients are listed in Table 2. Chromosomal instability in the form of multiple chromosomal breaks and greater than two nonclonal rearrangements preceded the appearance of clonal abnormalities in 4 of the patients.

The clinical findings varied greatly at the time the initially abnormal chromosomess were first detected after BMT. Frank AML was present in 2 patients (cases no. 1 and 10), and morphologically diagnosable MDS was seen in 3 (cases no. 3, 4, and 5). In all 5 of the patients with clinically and pathologically evident hematologic disease, the vast majority of cells examined displayed abnormal chromosomes: 1 with topoisomerase II-related changes, 2 with classical-form MDS karyotypic findings, and 2 with a combination of both types. Four of these five patients have died, all from complications of AML or MDS. The time of death ranged from 1 to 6 months (mean, 2 months) after the onset of BM disease. One patient is still alive with both recurrent HD and MDS 3 years after BMT.

There were no definite clinical or pathologic features of hematopoietic disease in the remaining 5 patients at the time clonal cytogenetic abnormalities were first detected. In fact, the chromosomal changes were discovered in these patients only through the frequent use of cytogenetic studies performed during posttransplantation follow-up visits. Nearly all of the cells from 1 patient (case no. 9) contained a clonal 2p abnormality, a finding that was confirmed on repeat studies. This patient has continued to show no signs or symptoms of MDS, and the bone marrow has remained free of lymphoma, 4 months after discovery of the abnormal cytogenetics. However, lymphoma has recurred in a lymph node. In
the 4 remaining patients without clinically or pathologically evident MDS (cases no. 2, 6, 7, and 8), the initial clonal cytogenetic abnormality involved less than half of the cells examined. Repeat examinations have shown an increase in the number of clonally abnormal cells in all of these patients; 1 with classic-type MDS cytogenetics still has no evidence of disease, 2 (1 with topoisomerase I1 and 1 with classic MDS changes) have developed cytopenia without convincing morphologic features of MDS, and 1 with topoisomerase II type changes has died of recurrent NHL.

**Statistical analysis.** Using a control group matched for disease and length of follow-up, there was no statistically significant association between the development of clonal cytogenetic abnormalities and age, number of chemotherapeutic regimens administered for the primary disease, prior local radiation, BMT conditioning regimen (with or without TBI), or type of lymphoma ($P > .29$ for all variables). Although the source of stem cell support was also not a statistically significant risk factor, there was a trend for decreased risk with the use of BM, alone or in combination with PBSCs, compared with the use of PBSCs alone (relative risk $= 0.28$, $P = .07$). The difference in probability of overall survival for patients with only cytogenetic abnormalities was not significantly better than those with clinically and pathologically evident MDS or AML ($P = .15$), but follow-up is short, particularly for those with no clinical disease (range, 3 to 12 months). Based on Kaplan-Meier product limit estimates, there is approximately a $9\% \pm 4.7\%$ risk of developing abnormal chromosomes within 8 years of induction therapy, or within 3 years of auto-BMT (Fig 2).

### DISCUSSION

Recurrence of the original neoplasm is the most common cause of failure after auto-BMT for malignant disease. Secondary malignancies are much less frequent. In fact, the development of an acquired hematopoietic stem cell disorder after auto-BMT has been previously described in only 9 patients, with preliminary data on more patients recently reported in abstract form. In this study, we describe the development of clonal karyotypic changes in 10 patients who had undergone autologous BM rescue. These changes were associated with recognizable MDS or AML in 5 of the patients, establishing secondary hematopoietic malignancy as a significantly morbid complication of auto-BMT. The patient cohort was derived from a group of 275 individuals who underwent high-dose chemotherapy followed by autologous marrow rescue for malignant lymphoma over a period of 6 years. To eliminate the possibility that the AML or MDS detected in these patients was in fact a manifestation of recurrent disease, patients who had originally received transplant MDS and AML, the presence of normal chromosomes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>BM Karyotype*</th>
<th>Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46,XX.t(16;21)(q24;q22) [20]</td>
<td>AML</td>
</tr>
<tr>
<td>2</td>
<td>46,XY,der(?)(del?)q22?inv?(?)(p13q22),del(20)(q11q13.3) [8]</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Sdl 1: 42,iderm.+1,+6,+8,+9,+11,+18,+22 [3]</td>
<td>MDS</td>
</tr>
<tr>
<td>4</td>
<td>Sdl 2: 44,iderm,dic(6;21)(p21.3;q22)del(6)(q23q25),del(7)(q32q36),del(10)(q22q23).</td>
<td>MDS</td>
</tr>
<tr>
<td>5</td>
<td>Sdl 2: 46,XX,-7,+mar1,+mar2 [cp7]</td>
<td>MDS</td>
</tr>
<tr>
<td>6</td>
<td>Composite karyotype: 46-47,XY,der?(1)(t;7;7),t(X;15)(q22;q11.2) [21],del(21)(p13)</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>46,XY,del(11)(q13q24) [3]</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>46,XY,del(11;15)(q23;22) [3]</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>46,XY,del(11;15)(q23;22) [3]</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>Sdl 1: 46,iderm,+mar [6]</td>
<td>AML</td>
</tr>
<tr>
<td>13</td>
<td>51,XY,+8,+11,+12,+15,+21 [1]</td>
<td>AML</td>
</tr>
</tbody>
</table>

Although 2 of the 5 patients without diagnosable BM disease have developed cytopenia, none show pathologic evidence of MDS or AML, 8 months (median) after the abnormal chromosome studies. Abbreviations: Dx, pathologic diagnosis rendered at the time of cytogenetic study; Sdl, sideline.

*The results of the initially abnormal karyograms post-BMT are given.
at the time of marrow harvest does not fully negate the risk of developing subsequent hematopoietic cell abnormalities. The cytogenetic changes detected after auto-BMT were typical of those previously described for therapy-induced hematopoietic disease.17–19 Chromosomes 5 and 7 were most often affected, with less frequent alterations seen in a variety of other chromosomes. These abnormalities have been strongly associated with the use of chemotherapeutic drugs, typically alkylating agents, especially when administered in multicycle, multidrug regimens or with radiation therapy. In addition, 11q23 and 21q22 chromosomal abnormalities have recently been associated with MDS and AML after the use of topoisomerase II inhibitors such as VP-16,20–22 which is a common component of both the multidrug regimens used in the treatment of leukemia and lymphoma and the conditioning regimens used for BMT. Only 1 patient in this study did not have the typical clonal chromosomal abnormalities characteristic of either the classic or topoisomerase-II related MDS types. However, alterations of the short arm of chromosome 2 like those seen in this patient have been previously reported in both MDS and AML.23

The vast majority of patients developing clonal cytogenetic abnormalities (9 of 10) were exposed to multiple different treatment regimens encompassing a variety of chemotherapeutic agents as a consequence of repeated disease relapses before the time of BM harvest. Half of the patients also received local radiation treatments. The cytogenetic abnormalities detected were therefore in keeping with the heavy exposure to the multiple therapies these patients experienced. Furthermore, the temporal relationship of induction therapy to the development of karyotypic abnormalities (mean, 3.9 years) is similar to the time intervals previously reported for therapy-induced hematopoietic disease in patients who did not undergo BMT, which usually average 4 to 7 years.17,24–27 The interval from the time of BMT to the development of abnormal chromosomes was much shorter, ranging from 0.5 to 3.1 years (mean, 1.4 years).

In the patient group reported here, the cumulative probability of developing clonal cytogenetic changes relative to induction therapy was approximately 9% at 8 years, identical to the risk previously reported in large series of patients treated for HD or NHL.23,24 Therefore, both the interval between induction therapy and the onset of disease and the cumulative risk of disease are similar to previously reported studies performed on patients not subjected to transplantation. This suggests that the development of abnormal cytogenetics in patients treated with auto-BMT for lymphoma may primarily result from exposure to toxic agents before the time of transplant. However, the possible potentiating effect of BMT in this process is uncertain, and cannot be entirely ignored, because all patients in this study had normal BMs, as determined by clinical, pathologic, and cytogenetic studies, immediately before harvest. Whether this represents a failure of routine cytogenetic analysis to detect the existence of occult hematologic disease, or the added exposure of residual patient stem cells to high-dose chemotherapy and radiation during the process of BMT induces the changes, is unclear. Our retrospective studies were primarily observational, and the relative contribution of BMT to the ultimate development of clonal hematopoietic alterations in these patients cannot be accurately assessed.

Although the cytogenetic abnormalities detected were typical of those previously described for therapy-induced AML and MDS, the pathologic and clinical features of some of the patients were not characteristic. As classically described, therapy induced hemopathy occurs 4 to 7 years after therapy and manifests pathologically as profound trilineage myelodysplasia.28,29 Clinically, there is often a brief period of pancytopenia followed by rapid evolution to acute leukemia that is relatively resistant to therapy. Median survival is typically 4 to 8 months, even in the absence of frank leukemia.17,27–29

Four of the five patients with clinical and pathologic evi-
idence of MDS or AML behaved in this fashion. Only 1 patient with morphologically diagnosable disease at the time of the first abnormal cytogenetic studies post-BMT has survived more than 1 year, and is still alive with both MDS and recurrent HD. The other 5 patients had unexpectedly abnormal karyograms detected in routine follow-up visits, and have experienced a more indolent course. As opposed to those with clinically and pathologically evident disease, the clonal abnormalities in 4 of these 5 patients involved less than half of the cells examined in the initial studies. On subsequent analyses, the number of clonally abnormal cells increased, a finding that is consistent with clonal expansion. However, with a median follow-up of 8.5 months, only 2 patients have developed cytopenia, 1 has died of recurrent lymphoma without developing hematologic abnormalities, and the remaining 2 still show no evidence of disease. The performance of frequent post-BMT cytogenetic studies in these patients may have identified an early, but progressive, stage of therapy-induced myelodysplastic disease that is not readily identified with conventional criteria. Although the short-term behavior appears different from that of classically described secondary MDS, long-term follow-up will be required to determine the significance of these findings. Studies on this apparently indolent form of MDS are currently in progress.

Using a control group of patients matched for disease, length of follow-up, and treatment with auto-BMT, a variety of parameters were statistically analyzed in an attempt to identify risk factors predictive for the development of clonal cytogenetic abnormalities, but none was found. There was an increased risk that approached statistical significance with the use of PB as a source of stem cells support, but analysis of more patients will be required to know the full importance of this finding. Pretransplant cytogenetic studies will spare some patients from BMT failure caused by secondary MDS or AML, but this study suggests that individuals destined to develop abnormal karyotypic clones after auto-BMT, with or without recognizable AML or MDS, cannot be prospectively identified. There may be an incalculable susceptibility factor that primarily determines an individual’s risk, very much like the situation that exists after intensive therapy for a wide variety of malignant diseases.

REFERENCES


Clonal karyotypic hematopoietic cell abnormalities occurring after autologous bone marrow transplantation for Hodgkin's disease and non-Hodgkin's lymphoma

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