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Therapy-related myeloid leukaemia: A model for leukemogenesis in humans

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Abstract

Therapy-related myeloid leukemia (t-AML) is a distinctive clinical syndrome occurring after exposure to chemotherapy (CT) or radiotherapy (RT). We studied 306 consecutive patients referred to the University of Chicago with cytogenetic analyses. Since 1972, 141 males and 165 females with a median age of 51 years (range: 3–83 years) at primary diagnosis and 58 years (range: 6–86 years) at secondary diagnosis were analyzed. Patients had received various cytotoxic agents including alkylating agents (240 patients, 78%) and topoisomerase II inhibitors (115 patients, 39%). One hundered and twenty-one (40%) had received CT alone, 43 (14%) had received RT alone, and 139 (45%) had received both modalities. At diagnosis of t-AML, 282 (92%) had clonal abnormalities involving chromosome 5 ($n = 63$), chromosome 7 ($n = 85$), both chromosomes 5 and 7 ($n = 66$), recurring balanced rearrangements ($n = 31$), or other clonal abnormalities ($n = 39$); 24 had a normal karyotype. Abnormalities of chromosomes 5 and/or 7 accounted for 76% of all cases with an abnormal karyotype. Seventeen patients had developed t-AML after autologous stem cell transplantation, but no unique pattern of cytogenetic abnormalities was observed. Patients presenting with acute leukemia were more likely to have a balanced rearrangement than those presenting with myelodysplasia (28% versus 4%, $p < 0.0001$). Shorter latency was observed for patients with balanced rearrangements (median: 28 months versus 67 months; $p < 0.0001$). Median survival after diagnosis of t-AML was 8 months; survival at 5 years was less than 10%. To gain insights into the molecular basis of this disease, we performed gene expression profiling of $CD34^+$ hematopoietic progenitor cells from t-AML patients. We found distinct subtypes of t-AML that have characteristic gene expression patterns. Common to each of the subgroups are gene expression patterns typical of arrested differentiation in early progenitor cells. Leukemias with a −5/del(5q) have a higher expression of genes involved in cell cycle control (*CCNA2*, *CCNE2*, *CDC2*), checkpoints (BUB1), or growth (MYC), and loss of expression of the gene encoding interferon consensus sequence-binding protein (*ICSBP*). A second subgroup of t-AML is characterized by down-regulation of transcription factors involved in early hematopoiesis (*TAL1*, *GATA1*, and *EKLF*) and overexpression of proteins involved in signaling pathways in myeloid cells (*FLT3*) and cell survival (*BCL2*). Establishing the molecular pathways involved in t-AML may facilitate the identification of selectively expressed genes that can be exploited for the development of targeted therapies.

Keywords: Therapy-related myeloid leukaemia ;Cytogenetic analysis ;Leukemogenesis

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1. Introduction

Therapy-related myelodysplasia and myeloid leukemia (t-MDS/t-AML) is a well-recognized clinical syndrome occurring as a late complication following cytotoxic therapy [1–5]. These neoplasms are thought to be the direct consequence of mutational events induced by cytotoxic therapy. Several distinct cytogenetic and clinical subtypes of t-MDS/t-AML are recognized that are closely associated with the nature of the preceding treatment. The latency between primary diagnosis and therapy-related disease ranges between several months to several years, and may be dependent on the cumulative dose or dose intensity of the preceding cytotoxic therapy, as well as the exposure to specific agents. A spectrum of morphologic abnormalities is observed [6]. There is a continuum in the percentage of marrow blasts from a myelodysplastic syndrome (t-MDS) to overt acute myeloid leukemia (t-AML).

The majority of patients with t-MDS/t-AML have clonal chromosome abnormalities in their bone marrow cells at diagnosis [1–5,7–14]. Between 1972 and July 2001, 306 consecutive patients referred to the University of Chicago were confirmed to have a diagnosis of t-MDS/t-AML after clinical and morphologic review in our laboratories [7]. All patients had received chemotherapy (CT), radiation therapy (RT), or a combination of these for an antecedent disorder. The latency interval was defined as starting with the first cytotoxic therapy and ending with the first bone marrow exam showing therapy-related MDS or myeloid leukemia. Chemotherapy agents were classified by mechanism of action and included alkylating agents (melphalan, cyclophosphamide, nitrogen mustard, etc.), topoisomerase II inhibitors (etoposide, doxorubicin, daunorubicin, mitoxantrone, etc.), anti-metabolites (fluorouracil, methotrexate, 6-mercaptopurine, etc.), and anti-tubulin agents (vincristine, vinblastine, paclitaxel, etc.).

2. Clinical characteristics

The clinical characteristics of the 306 t-MDS/t-AML patients are shown in Table 1.

There were 171 (56%) patients with a primary hematologic malignancy, with nearly equal numbers of patients with Hodgkin lymphoma (or Hodgkin disease, (HD), 77; 25% of the entire series) and non-Hodgkin lymphoma (NHL, 70; 23%). One hundred and seventeen (38%) patients had a solid tumor as the primary malignancy. Breast cancer was the most common among these (32 patients; 10%). Importantly, we also studied 18 (6%) patients who had not had a prior malignancy. However, these patients had received cy-

Table 1
Primary diagnoses and primary cytotoxic therapy received by 306 patients in whom therapy-related myeloid leukemia developed

Primary diagnosis	No. of patients	Chemotherapy only (%)	Radiotherapy only (%)	Combined modality therapy (%)
No malignancy	18	12 (67)[a]	2 (11)	4 (22)
Hematologic malignancy	171	69 (40)	5 (3)	97 (57)
Hodgkin lymphoma	77	18 (23)	4 (5)	55 (71)
Non-Hodgkin lymphoma	70	33 (47)	1 (1)	36 (51)
Myeloma	23	17 (74)	0	6 (26)
Other	1	1 (100)	0	0
Solid tumor	117	40 (35)	36 (32)	38 (33)
Breast	32[b]	11 (35)	5 (16)	15 (48)
Ovary	15	12 (80)	1 (7)	2 (13)
Prostate	13[b]	0	11 (100)	0
Lung	9	5 (56)	2 (22)	2 (22)
Cervix	7	0	4 (57)	3 (43)
Other[c]	41	12 (30)	13 (32)	16 (39)
Total	306[b]	121 (40)	43 (14)	139 (46)

[a] Numbers in parentheses are percentages for each row of data according to primary therapy.
[b] In three patients, the primary therapy was incompletely known.
[c] Smaller diagnostic groups were not further subdivided by primary therapy.