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Clinically silent clonal cytogenetic abnormalities arising in patients treated for lymphoid neoplasms

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ABSTRACT

Newly emerged clonal cytogenetic abnormalities (CCA) in patients with prior cytotoxic therapy are highly concerning for therapy-related myeloid neoplasms (t-MN). In some patients, however, CCA appeared to be clinically "silent". In this study, we describe 25 patients who developed CCA after they received cytotoxic therapies for lymphoid neoplasms but never developed t-MN. These clinically "silent" CCA were always present as single abnormalities, often detected in a small subset of cells, and tended to disappear over time. We conclude that the occurrence of CCA is not always associated with t-MN. Clinical correlation is essential to guide a proper management of these patients.

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1. Introduction

Therapy-related myeloid neoplasms, including therapy-related acute myeloid leukemia (t-AML), myelodysplastic syndromes (t-MDS) and myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN), can occur as a late complication of cytotoxic chemotherapy and/or radiation therapy for a prior neoplastic or non-neoplastic disorder [1]. Cytogenetic abnormalities can be detected in over 90% of these patients [1]. Therapy-related myeloid neoplasms (t-MN) secondary to alkylating agents or ionizing radiation occur approximately 5–10 years after exposure, and are commonly associated with unbalanced loss of genetic material (chromosomes 5 and/or 7 most often). On the other hand, t-MN after DNA topoisomerase II inhibitor therapy often arise 1–5 years after exposure, and are commonly associated with balanced translocations involving chromosome 11q23 and *MLL* gene rearrangement. In general, patients with t-MN have a very poor clinical outcome.

Clonal cytogenetic abnormalities (CCA) are defined as chromosomal structural abnormalities or numerical gain in at least two metaphases, or numerical loss in at least three metaphases, or an abnormality in a single metaphase but confirmed by other methods, such as fluorescence in situ hybridization (FISH). Chromosomal abnormalities often occur at a high frequency during or immediately following high-dose chemotherapies [2,3] or autologous stem cell transplant (SCT) [4]. These abnormalities, however, are often transient, non-clonal and are thought to be random events that reflect an immediate therapy-related genotoxicity. These non-clonal cytogenetic abnormalities are known to not predict the development of t-MN. On the other hand, CCA that are detected in patients after exposure to cytotoxic therapies raise the specter of t-MN, especially when CCA persist in the follow-up bone marrow (BM) specimens. T-MN is a serious complication of cytotoxic therapy that often affects the patient's treatment plan for primary cancer and requires appropriate management for t-MN, including allogeneic SCT.

During the sign-out of conventional cytogenetics tests in a clinical laboratory, we have noticed that some patients develop CCA in BM and yet did not develop t-MN with a close follow-up. Here we refer to these CCA as clinically "silent" CCA. It would be of great clinical importance to understand the frequency and the features

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of these "silent" CCA, and how they are different from the "deleterious" CCA which are associated with t-MN.

2. Material and methods

2.1. Patients

We searched the database of the Clinical Cytogenetics Laboratory at The University of Texas MD Anderson Cancer Center (UT MDACC) during 2002–2012 for CCA in patients who had received cytotoxic therapy for lymphoma or plasma cell myeloma and underwent BM re-staging. To avoid "transient" chromosomal alterations as a direct result of genotoxic effects of cytotoxic therapies, all patients were assessed at least 3 months after the last dose of cytotoxic therapy. Cases without clinical or laboratory follow-up after the detection of CCA were not included. We further limited the inclusion criteria to patients who had no morphologic evidence or only minimal involvement of the BM by lymphoma or plasma cell myeloma at the time of CCA detection. Minus Y (−Y) as a sole abnormality was not included, since it may only represent age-related effect [5]. The study was approved by the institutional review board of our hospital.

2.2. Laboratory data and bone marrow assessments

Peripheral blood (PB) smears, BM aspirate smears and BM trephine biopsy specimens were reviewed. All cell lineages in PB and BM were evaluated for morphologic evidence of dysplasia. BM cellularity and the percentage of blasts in PB and BM were assessed. The involvement of BM by primary lymphoma or plasma cell myeloma was evaluated by morphology, immunohistochemistry and/or flow cytometry immunophenotyping analysis (FCI). Complete blood cell counts (CBC) at the time of CCA detection and during the follow-up were reviewed. FCI analysis using a panel designed to detect MDS was performed as described previously [6].

2.3. Conventional chromosomal analysis and fluorescence in situ hybridization (FISH)

Conventional chromosomal analysis was performed on G-banded metaphase cells prepared from unstimulated 24-h and mitogens stimulated 72-h BM aspirate cultures using standard techniques. Mitogens included 12-O-tetradecanoylphorboM 3-acetate (TPA), interleukin 4 (IL-4), and lipopolysaccharide (LPS). Twenty metaphases were analyzed and the results were reported using the International System for Human Cytogenetic Nomenclature (ISCN 2013) [7]. Confirmation FISH was performed in a subset of cases using the corresponding specific probes using protocols routinely used in the clinical cytogenetics laboratory.

2.4. Statistical analysis

Column statistics was used for numerical variables. The latency interval from prior cytotoxic therapy to the emergence of CCA was calculated from the time of initiation of cytotoxic therapy to the time of CCA detection. The length of CCA persistence was calculated from the initial time of CCA detection to the time of CCA disappearance or to the time of the last follow-up, if CCA is persistent.

3. Results

3.1. Patients

Over a 10-year period (2002–2012) at our institution, approximately 2500 patients underwent bone marrow examination with conventional cytogenetic analysis after they received cytotoxic therapies for either lymphoma or myeloma. CCA were detected in a total of 123 patients who had no or minimal primary lymphoma/myeloma involvement. Twenty-one patients fulfilled diagnostic criteria for t-MDS and 102 patients showed no clinical or morphological evidence of t-MDS. Among the latter group, 25 patients did not show evidence of t-MN during a median follow-up of 36 months, and formed this study group. All other patients with CCA were excluded from the study for the following reasons: 15 patients demonstrated diagnostic evidence of t-MN in a follow-up biopsy specimens; 41 patients had no further clinical or cytogenetics follow-up; 12 patients had relapsed disease and re-started the cytotoxic therapy within 6 months; and 9 patients underwent allogeneic SCT within 3 months.

There were 18 male and 7 female patients, with a median age of 60 years (2–78). The antecedent neoplasms included plasma cell myeloma (PCM, $n = 10$), follicular lymphoma (FL, $n = 5$), mantle cell lymphoma (MCL, $n = 4$), diffuse large B cell lymphoma (DLBCL, $n = 3$), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL, $n = 1$), Burkitt lymphoma ($n = 1$) and classical Hodgkin lymphoma (CHL, $n = 1$). At time of initial staging, all patients with PCM and CLL/SLL had BM involvement as well as 1 patient with DLBCL (case #5), 3 patients with FL (cases #8, 9, 10), 1 patient with MCL (case #12), and 1 patient with Burkitt lymphoma (case #1) (Table 1).

All patients had received chemotherapy regimens, 4 patients also received radiation therapy (cases #11, 15, 16, 18) and 20 patients received autologous SCT (Table 1). The mainstay chemotherapy regimens included FCR (fludarabine, cyclophosphamide, rituximab) for CLL/SLL; R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) for FL and MCL; R-Hyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, mesna, methotrexate, leucovorin) for DLBCL and MCL; ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for CHL; and melphalan, cyclophosphamide, vincristine, doxorubicin, and various steroids for PCM.

3.2. Cytogenetics findings

Baseline cytogenetic data from BM (at the time of lymphoma/myeloma diagnosis, prior to chemotherapy) were available in 20/25 (80%) patients. Fifteen patients had a normal karyotype, 2 patients (cases #2, 23) showed isolated–Y, patient #1 showed a clone of t(8;14)(q24.1;q32) corresponding to Burkitt lymphoma; patients #16 and #24 showed a hyperdiploid clone corresponding to PCM.

The median interval from the first dose of chemotherapy to the detection of CCA was 62 months (range 7–112). None of the patients was in the middle of or immediately post cytotoxic therapy when CCA were detected. All the CCA were present as single and newly detected abnormalities, either structural or numerical, including del(20q) ($n = 8$), del(11q) ($n = 2$), del(5q) ($n = 2$), +15 ($n = 2$), +Y ($n = 1$), +8 ($n = 1$), del(9p) ($n = 1$), r(7) ($n = 1$), del(7q) ($n = 1$), inv(5) ($n = 1$) and balanced translocations ($n = 5$). The percentage of metaphases with CCA in BM ranged from 10 to 80% (median 20%, 4 of 20 metaphases) (Table 1). FISH studies were performed in 14 cases (cases #1, 3, 5, 6, 9, 11, 12, 14–18, 22, 24) using the corresponding probes: CEP8 for +8, EGR1/D5S721, D5S23 for del(5q); D7S522/CEP7 for del(7q) and r(7); D20S108 for del(20q); and MLL dual color, break-apart probe for 11q23 translocation. All karyotypic abnormalities were confirmed, and no *MLL* gene rearrangement was noted.

For comparison, the cytogenetics abnormalities in 36 patients who developed t-MDS (21 patients diagnosed with t-MDS at the time when the CCA were detected, and 15 patients developed t-MDS during the follow-up) are listed in Supplementary table

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