Original Study

Clinical Significance of Acquired Cytogenetic Clones in Patients With Treated Follicular Lymphoma

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Abstract

Secondary malignancies like therapy-related myeloid neoplasms are becoming an important issue in follicular lymphoma survivors. We reported 25 treated follicular lymphoma patients who developed new cytogenetic abnormalities. Our results indicate that silent acquired cytogenetic clones are a common phenomenon in these patients. Risk stratification of secondary malignancy in these patients was discussed.

Background: Follicular lymphoma (FL) is the second most common B-cell non-Hodgkin lymphoma worldwide. In most patients, the disease is diagnosed at advanced stages and cannot be cured using conventional therapeutic approaches. To assess the role of cytogenetic abnormalities in therapy-related myeloid neoplasms (tMNs), we studied the clinicopathologic and cytogenetic features of treated FL patients who subsequently developed a new acquired cytogenetic clone (ACC). **Patients and Methods:** Twenty-five treated FL patients developed new cytogenetic abnormalities from 2009 to 2012. Patients were divided into 3 groups based on the presence and absence of tMNs: group 1, ACC without tMNs after a median follow-up of 15 months; group 2, ACC with possible tMN after silent ACC detection; group 3, tMNs present at the first ACC detection. **Results:** The most frequent cytogenetic aberrations involved chromosome 7. Compared with group 1, group 3 had significantly greater size of ACC, higher frequency of chromosome 7 aberrations, more likely showed dysplasia, and lower platelet count ($P = .03$). **Conclusion:** Our results indicate that the presence of ACC alone is insufficient for diagnosis of tMNs. The proportion of cells with specific aberrations at first ACC, bone marrow dysplasia, and low platelet counts might predict outcome of ACC.

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Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma and the second most frequent B-cell non-Hodgkin lymphoma subtype worldwide. It generally has a long natural history and multiple remissions and relapses.[1] Because the improvement of treatment regimens[2,3] have increased the expected survival duration of FL patients, secondary malignancies like therapy-related myeloid neoplasms (tMNs) are becoming an important issue in FL survivors. Risk stratification of FL survivors based on new acquired cytogenetic clones (ACCs) is thus becoming clinically important for earlier diagnosis and management of tMNs.

There are very few studies about therapy-related neoplasms in treated FL patients. Gopal et al[4] evaluated patients with relapsed FL and reported an incidence of 7.6% for therapy-related myelodysplastic syndrome (tMDS) or therapy-related acute myeloid leukemia (tAML) at 8 years in a high-dose radioimmunotherapy group and 8.6% at 7 years for a group who received conventional high-dose therapy. In a clinical trial of FL, Ladetto et al[5] reported a cumulative incidence of 1.7% of tMDS/tAML at 4 years for patients who had received CHOP-R (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone, and rituximab) therapy.

More than 90% of patients with tMDS have an abnormal cytogenetic clone.[6,7] The most common clonal cytogenetic

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abnormalities detected in tMDS/tAML involve loss of chromosome 5 or 7 (or both) or deletion of the long arm of these chromosomes.[8] In the 2008 World Health Organization (WHO) classification,[9] del(7q), del(5q), and del(13q) (or its related monosomy, −7, −5, and −13, respectively) are considered presumptive evidence for myelodysplastic syndrome (MDS) in the presence of refractory cytopenia; whereas del(20q) as a sole abnormality with no morphologic criteria met is not considered sufficient evidence for MDS. However, there is still disagreement and confusion among pathologists and clinicians on how and when to make a definite diagnosis of MDS on the basis of clonal cytogenetic abnormalities and clinical data in the absence of definite morphologic evidence of dysplasia. Some patients have unremarkable morphologic features in bone marrow (BM) but harbor unexpected clonal cytogenetic abnormalities.[10,11] ACCs associated with the development of tMDS have been incidentally observed in patients treated for lymphoma[12]; we previously proposed the concept of "silent ACC" (SACC) to describe these clones (Figure 1).[13] Moreover, the latency period from the emergence of ACCs to the diagnosis of tMN and the relationship of the frequency of mutant alleles with the outcome of the disease are not well defined.

Here we report our findings from a retrospective study of 25 patients who had been treated for FL and then developed new ACCs. We discuss the clinical and pathological features and outcomes of these cases.

Patients and Methods

Patients

We retrospectively reviewed cases of patients who had been treated for FL and subsequently developed new ACCs between June 1, 2009 and June 1, 2012 at The University of Texas M.D. Anderson Cancer Center (MDACC). The diagnosis of FL and tMN had been made according to criteria established by the WHO.[9] This study was approved by the MDACC institutional review board. A detailed chart review was conducted for each identified patient. Treatment for FL was categorized as chemotherapy, radiotherapy, or both. The type of chemotherapy was categorized as alkylating agent, purine analogue, anthraquinone, rituximab, or other.

Cytogenetic Analyses

Conventional cytogenetic analysis was performed according to the protocols used in our clinical cytogenetics laboratory as previously described,[14] including collection of BM samples through cell culture without any stimulant for 24 or 48 hours, cell harvesting, slide-preparation for G-banding, or fluorescent in situ hybridization (FISH). For most patients, 20 metaphase cells, if available depending on the sample quality and quantity for cell cultures, were analyzed. The results were reported using the International System for Human Cytogenetic Nomenclature.[15]

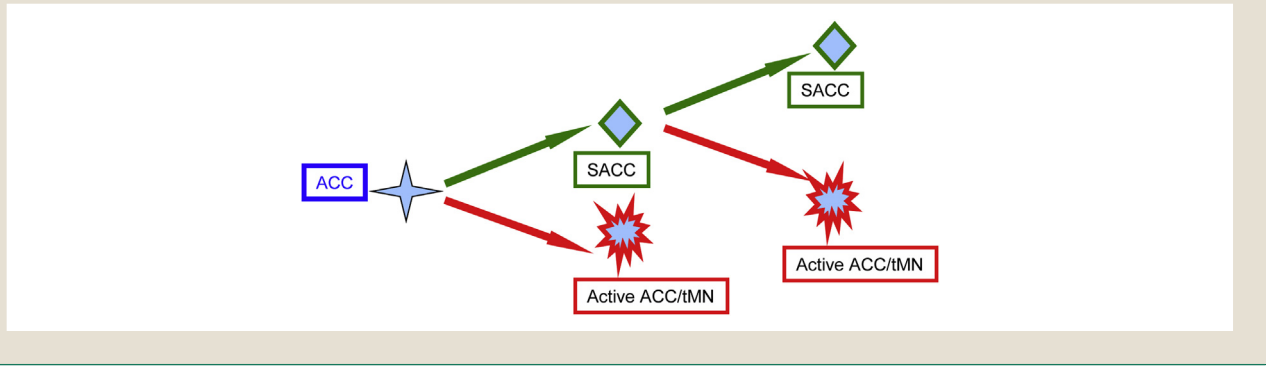
For specification of chromosomal abnormalities with structural changes, deletion involving 7q31/D7S522, 20q12/D20S108, 13q14/Rb1, and 5q31/EGR1, were classified as del(7q), del(20q), del(13q), and del(5q), respectively. Therefore, FISH analysis[16] was performed using an LSI RB1 probe, and a D20S108 probe (Abbott Molecular, Inc), which hybridized to band 13q14, and band 20q12, respectively; whereas FISH analysis for del(5q), and del(7q) was performed using LSI EGR1/D5S23, D5S721 dual-color probes, and D7S522/CEP7 dual-color probes, respectively. Commercially available dual-color, dual-fusion translocation probes IGH/BCL2 (Abbott/Vysis, Des Plaines, IL) were used to detect the presence of t(14;18)(q32;q21) associated with FL. A total of 200 interphases were analyzed for each probe according to the protocols used in our clinical cytogenetics laboratory, and a cutoff for each FISH probe was used according to the FISH protocols in the Clinical Cytogenetics Laboratory at MDACC.

Laboratory Data and BM Assessment

Our criteria for SACC were: (1) the presence of ACC, first detected in routine cytogenetic analysis then confirmed using FISH analysis accordingly; (2) no evidence of myeloid disease, confirmed using BM morphologic evaluation at the time of the occurrence of ACC; and (3) no clinical manifestation of secondary disease at the time of the occurrence of ACC. We evaluated the corresponding BM biopsy specimens for tMN at the time of detection of ACC.

We categorized the patients according to their ACC and biopsy results: group 1, SACC without tMN development after a median follow-up of 15 months; group 2, SACC with possible tMN development after SACC detection; and group 3, tMN development at the time of ACC detection.

Figure 1 Silent ACC and tMN Development



Abbreviations: ACC = acquired cytogenetic clone; SACC = silent acquired cytogenetic clone; tMN = therapy-related myeloid neoplasm.