Original Study

Jumping Translocations in Myeloid Malignancies Associated With Treatment Resistance and Poor Survival

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Abstract

Jumping translocations (JT) are rare cytogenetic abnormalities occurring in several types of cancer, including myeloid malignancies. We identified 10 cases of myeloid malignancies associated with a JT in our cytogenetic database. The acquisition of a JT appeared to be a late event and most patients failed treatment with chemotherapy and had a relatively short survival after identification. The occurrence of a JT may be associated with poor prognosis in myeloid malignancies.

Background: Jumping translocations (JT) are uncommon cytogenetic abnormalities involving nonreciprocal translocations of a single donor chromosome onto 2 or more chromosomes. The clinical characteristics and prognosis of JTs in patients with myeloid malignancies are not well described. **Materials and Methods:** We searched our cytogenetic database from 2003 to 2014 to identify cases of myeloid malignancies associated with a JT. These cases were cross-referenced with our clinical databases to determine patient characteristics, response to treatment and overall survival. **Results:** We identified 10 patients with myeloid malignancies and a JT: 4 cases of acute myeloid leukemia with myelodysplastic syndrome–related changes, 4 cases of myelodysplastic syndrome, and 2 cases of postpolycythemia myelofibrosis. The donor segment was derived from chromosome 1 in every case. The acquisition of a JT was a late occurrence, with a median time to JT development of 24.9 months (range, 0-248 months) from diagnosis. The overall response to treatment was poor, with no patients experiencing a response to conventional chemotherapy or hypomethylating agents. The median overall survival for the group was 9 months (95% confidence interval, 2.5-15.5) after identification of a JT. **Conclusion:** The acquisition of a JT in patients with myeloid malignancies appears to be a late event and is associated with myelodysplasia. In our series, this was associated with a poor prognosis with a poor response to treatment, disease transformation to acute myeloid leukemia, and short overall survival.

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Introduction

Jumping translocations (JT) are nonreciprocal chromosomal translocations of a single donor chromosome or chromosome fragment onto 2 or more recipient chromosomes.[1] This was first identified in Prader-Willi syndrome in the 1970s but has subsequently been described as an acquired cytogenetic change in several human cancers.[2] JTs are uncommon but have been repeatedly observed in solid and hematologic cancers, including several cases involving myeloid malignancies.[1,3-6] JTs involving chromosome 1 as the donor segment are the most frequently described, although the reason for this predilection is unknown. Several other chromosomes, including 3, 11, 15, and 21, have also been reported to act as a donor chromosome.[1,3,5,6] Case reports and small series of JTs in myeloid malignancies report poor outcomes; however, the implications of this unusual cytogenetic event are poorly understood. We report on a series of patients with myeloid neoplasms and JT with the goal of

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determining the clinicopathologic characteristics and response to treatment.

Methods

We searched our cytogenetic database for "jumping translocation" from the 2003 to 2014 to identify cases of JTs within our institution. This database was cross-referenced with a clinical database containing patient characteristics, treatments, and outcomes. Disease subtypes were classified according to the 2008 World Health Organization classification.[7] Response to treatment for acute myeloid leukemia (AML) was determined according to International Working Group (IWG) 2003 criteria, response for myelodysplastic syndrome (MDS) according to IWG 2006 criteria, and response for polycythemia vera (PV) and myelofibrosis (MF) according to IWG 2013 criteria.[8-11] Overall survival was calculated from the time of the first acquisition of a JT by the Kaplan-Meier method, and data were censored at death or last follow-up. Conventional chromosomal analysis was performed on G-banded metaphase cells from unstimulated 24-hour and 48-hour bone marrow aspirate cultures via standard techniques. Twenty metaphases were analyzed when possible; results were reported using the International System for Human Cytogenetic Nomenclature (ISCN 2013).[12]

Results

Baseline Clinical Characteristics and Prior Therapy

We identified 10 patients with myeloid neoplasms with a JT in our database from 2003 to 2014 (Tables 1-3). The database contained approximately 20,000 individual patient cases with myeloid neoplasms during this time period. At the time of JT identification, 4 patients had AML, 4 patients had MDS, and 2 patients had post–polycythemic myelofibrosis (post-PV-MF). Of the 4 patients with AML, all were classified as AML with myelodysplasia-related changes, and 2 had a preceding diagnosis of MDS. Both patients with post-PV-MF had the JAK2 V617F mutation. Only 1 patient had a JT identified by cytogenetic analysis at the time of their initial diagnostic bone marrow examination. The median time from initial diagnosis to identification of a JT was 24.9 months (range, 0-248 months).

The individual treatments and corresponding responses before the identification of the JT are shown in Table 3. The median number of therapies before identification of a JT was 2 (range, 0-4), with only 1 patient not receiving treatment. Treatments before the development of a JT were diverse and included cytotoxic chemotherapy, hypomethylating agents, immunomodulatory drugs, targeted small molecule inhibitors, and growth factors. The 2 patients

Table 1 Clinical Features and Characteristics of Jumping Translocations

Patient No.	Disease	Age/Sex	Jumping Translocation		
			Interval (Months)[a]	Donor Chromosome	Recipient Chromosome
1	AML-MRC	63/F	1.4	1p22	3p21, 5q13, 11p15
2	AML-MRC	62/F	18.2	1q25	5q35, 6p25 17q36
3	AML-MRC	82/F	48.7	1q10	13q10, 14q10, 15q10
			49.6	1q10	15q10, 22q10
			52.4	1q10	13q10, 15q10, 22q10
			53.8	1q10	15q10, 22q10
			54.7	1q10	13q10, 15q10, 22q10
4	AML-MRC	44/M	12.7	1q21	Yp11.2, 6p25, 7q22, 10q22, 12q15
5	MDS-RCMD	75/M	23.0	1q11	Yq11.23, 12p11.2, 13p11.2, 16q11.1
			26.1	1q11	Yq11.23, 13p11.2, 16q11.2, 18q23
6	Therapy-related MDS	65/F	27.4	1q21	3p25, 13q34
			29.4	1q21	3p25, 6q26, 7q26, 13q34, 14p11.2, 18q22
			30.9	1q21	3p25, 13q34, 14p11.2
			32.0	1q21	3q25, 13q34, 14p11.2
7	MDS-RCMD	58/F	26.8	1p11	5p11, 13q11, 14p11, 18q21, 21p11.2, 22p11.1
			32.7	1p11	11q23, 14p11.2, 18q21.1, 21p11.2
8	MDS-RCMD	64/M	0	1q10/1q21	1p10, 19q23
			2.6	1q10	7p10, 14q10
			4.7	1q10	7p10, 14q10
			9.2	1q10	7p10
			11.3	1q10	7p10, 14q10, 19p10
9	Post-PV-MF	45/M	65.2	1q11	7p10, 9p10, 15p10
10	Post-PV-MF	67/F	248	1q11	8p23, 17p13
			259	1q11	8p23, 13p11.1, 15p11.1,17p12, 20p11.2

Abbreviations: AML-MRC = acute myeloid leukemia with myelodysplasia related changes; MDS = myelodysplastic syndrome; MF = myelofibrosis; PV = polycythemia vera; RCMD = refractory cytopenia with multilineage dysplasia.
[a]Interval indicates time from diagnosis to detection of jumping translocations.