Biological and Clinical Features of Trisomy 21 in Adult Patients With Acute Myeloid Leukemia

Paolo Strati, Naval Daver, Farhad Ravandi, Naveen Pemmaraju, Sherry Pierce, Guillermo Garcia-Manero, Aziz Nazha, Tapan Kadia, Elias Jabbour, Gautam Borthakur, Stefan Faderl, Alfonso Quintas-Cardama, Hagop Kantarjian, Jorge Cortes

Abstract

In non-Down syndrome (DS) adult acute myeloid leukemia (AML), trisomy 21 (+21) has traditionally been classified as intermediate-risk cytogenetic. We analyzed 90 adult patients with non-DS +21 AML treated between 1995 and 2011. Our analysis revealed that isolated +21 or +21 with favorable cytogenetic anomalies hitherto classified as intermediate-risk might in fact behave as favorable-risk cytogenetics in adult AML patients.

Introduction: Trisomy 21 is frequently noted in patients with AML. In adults, +21 has traditionally been considered an intermediate-risk cytogenetic aberration. **Patients and Methods:** We analyzed 90 patients with newly diagnosed AML harboring +21. Four cytogenetic subgroups were defined based on associated cytogenetic abnormalities: +21 alone, +21 with favorable, +21 with intermediate, and +21 with unfavorable cytogenetics. **Results:** Fifty-four percent of patients with +21 AML achieved a complete remission (CR) or CR with incomplete platelet recovery (CRp) after induction therapy with a trend toward improved CR/CRp rates in patients with +21 alone/+21 with favorable cytogenetics compared with patients with +21 with intermediate/+21 with unfavorable cytogenetics (76% vs. 50%; $P = .057$). Time to progression (TTP) was 12 months (range, 5-19) and overall survival (OS) was 9 months (range, 7-11) for the entire group. TTP was longer for patients with +21 alone (not reached) or with +21 with favorable cytogenetics (101 months) compared with those with +21 with intermediate cytogenetics (2 months) or +21 with unfavorable cytogenetics (11 months) ($P = .02$). Similarly, OS was improved in patients with +21 with favorable cytogenetics (not reached) or +21 alone (107 months), compared with +21 with unfavorable cytogenetics (9 months) or +21 with intermediate cytogenetics (8 months) ($P < .001$). The differences in TTP and OS were maintained on multivariate analysis ($P = .04$ and $P = .001$; respectively). **Conclusion:** Isolated +21 hitherto classified as intermediate-risk cytogenetics might actually behave as a favorable-risk cytogenetics in adult AML patients.

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Introduction

Trisomy 21 (+21) is a frequently identified chromosomal aberration in human neoplasms, particularly in acute myeloid leukemia (AML) wherein it is the second most frequent trisomy after trisomy 8.[1,2] Much of the literature regarding +21 in AML stems from the 10- to 20-fold increased risk of developing AML in patients with constitutional +21 or Down syndrome (DS).[3]

Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX

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Address for correspondence: Naval Daver, MD, Department of Leukemia, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 0425, Houston, TX 77030 Fax: 713-745-3920; e-mail contact: ndaver@mdanderson.org

In addition to the frequently identified +21, other numerical and structural anomalies involving chromosome 21 have been reported in patients with AML, albeit at lower frequencies.[4-7] Trisomy 21 has also been identified in the preleukemic phase of some AML cases,[8,9] suggesting that aberrations of chromosome 21 might function as "driver" or "second hit" events contributing to leukemogenesis. Cytogenetic analysis performed on large series of patients with AML have provided some insight into the epidemiology of acquired +21 in adult (United Kingdom Medical Research Council (AML) 11, AML 12, CALGB [Cancer and Leukemia Group B] 8461, SWOG/ECOG [Southwest Oncology Group/Eastern Cooperative Oncology Group])[10-13] and pediatric (AML 12, AML 10, Nordic Society of Paediatric Haematology and Oncology (NOPHO) 93, POG [Pediatric Oncology Group] 8821, Children's

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Cancer Study Group (CCG) 213)[13-18] populations. From these series it can be gleaned that +21 occurs with a frequency of 1% to 3%[12,13] in adults and 0 to 5%[15,18] in children. However, +21 patients comprised only a small part of the larger karyotypic analysis described in these large series and the specific role of +21 in acute myeloid leukemogenesis was not explored.

Trisomy 21 rarely occurs as an isolated anomaly (only 19%-26% of +21 AML cases) but is frequently noted to occur concomitantly with other chromosomal aberrations including trisomy 8 or complex karyotype in 38% of the cases and deletion 7 in 9% of the cases, respectively.[10,17,19,20] Small case series have hinted at a possible trend toward inferior outcomes in AML patients harboring isolated +21.[21-25] Clinically, these patients are characterized by increased expression of lymphocytic markers (namely CD7, CD9, and CD19) suggesting that leukemogenesis in these patients might occur at a more primitive or immature phase of hematopoesis.[26-29] Because +21 aberrations are frequently associated with other karyotypic abnormalities, the predictive and prognostic effect of isolated +21 on adult AML patients remains poorly defined. Hence, +21 aberrations have thus far been grossly subcategorized as intermediate-risk cytogenetics.

Lack of large series focusing on the role of +21 (either as isolated +21 or as +21 with other cytogenetic aberrations) in adult AML encouraged us to evaluate the biological and clinical features of this specific subgroup.

Patients and Methods

Patient Eligibility

We performed a retrospective analysis of non-DS +21 AML patients diagnosed with AML in accordance with the World Health Organization classification of hematopoietic tumors.[30,31] We included +21 AML patients who were diagnosed and treated at M.D. Anderson Cancer Center (MDACC) between January 1995 and December 2011. Patients with previous therapy for AML were excluded from the analysis. The baseline demographic and clinical characteristics, date of initial therapy, treatment modality, response to treatment, and long-term outcome for these patients were confirmed using manual chart review.

Cytogenetic Analysis and Cytogenetic Classification

Conventional cytogenetic analysis was performed using standard techniques on metaphase cells prepared from bone marrow aspirate specimens. For each patient, 20 Giemsa-banded metaphases were analyzed, and the results were reported using the International System for Human Cytogenetic Nomenclature.[32]

Cytogenetic subgroups were defined according to the classification schema proposed by Grimwade et al,[13] as "favorable" cytogenetics that included inv 16 (6 patients) and t(15;17) (1 patient); "intermediate" cytogenetics that included trisomy 8 (3 patients), del 20 (1 patient), trisomy 4 (1 patient), isodicentric X (1 patient), and trisomy 9 (1 patient); and "unfavorable" cytogenetics that included del 7 (2 patients), abn 11 (2 patients), and complex cytogenetics (61 patients).

Induction Regimens and Response Criteria

Induction regimens included idarubicin and cytarabine-based therapy (IA), fludarabine-based therapy (FLU), clofarabine-based therapy (CLO), topotecan-based therapy (cyclophosphamide, cytarabine, and topotecan [CAT]), hypomethylating agent-based therapy (HMT), and miscellaneous (including investigational) therapies (MISC).

Complete remission (CR) was defined by the presence of $\leq 5\%$ blasts in the bone marrow with $> 1.0 \times 10^9$/L neutrophils and $> 100 \times 10^9$/L platelets in the peripheral blood. CR with incomplete platelet recovery (CRp) included the same criteria as CR, but without recovery of the platelet counts to $\geq 100 \times 10^9$/L. Nonresponders (NRs) were defined as patients that failed to achieve CR or CRp. Time to progression (TTP) was defined as time from diagnosis to relapse or last follow-up. Overall survival (OS) was defined as time from diagnosis to death or last follow-up.

Table 1 Patient Characteristics (n = 90)

Characteristic	Median (Range) or n (%)
Age, years	59 (18-88)
Men	52 (58)
Race	
White	72 (80)
Black	7 (8)
Asian	1 (1)
Hispanic	7 (8)
Unspecified	3 (3)
White Blood Cell Count × 10^9/L	4.6 (0.6-190)
Hemoglobin, g/dL	8.6 (3.3-13.4)
Platelet Count × 10^9/L	53 (4-395)
Percentage of Blasts (Peripheral Blood)	17 (0-96)
Percentage of Blasts (Bone Marrow)	48 (0-97)
Morphological Subtype	
M 0-2	58 (64)
M 3	1 (1)
M 4-5	18 (10)
M 6	3 (20)
M 7	9 (4)
Granulocytic sarcoma	1 (1)
Cytogenetic Profile	
Trisomy 21 alone	11 (12)
Trisomy 21 plus favorable	7 (8)
Trisomy 21 plus intermediate	7 (8)
Trisomy 21 plus unfavorable	65 (72)
Mutation Analysis	
NPM1	1/25 (4)
NRAS	4/53 (7)
CKIT	0/26 (0)
FLT3	4/49 (8)

Statistical Considerations

Categorical and continuous variables were compared using either the χ^2 or Fisher exact tests, or the Mann-Whitney test, as appropriate. Survival curves were calculated using Kaplan-Meier