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

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Abstract

Introduction—Trisomy 21 (+21) is frequently noted in patients with acute myeloid leukemia (AML). In adults, +21 has traditionally been considered an intermediate-risk cytogenetic aberration.

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, +21 with unfavorable cytogenetics.

Results—Fifty-four percent of patients with +21 AML achieved a complete remission or complete remission with incomplete platelet recovery (CR/CRp) after induction therapy with a trend to improved CR/CRp rates in patients with +21 alone/+21 with favorable as compared to patients with +21 with intermediate/+21 with unfavorable (76% versus 50%; $p = 0.057$). 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) as compared to those with +21 with intermediate cytogenetics (2 months) or +21 with unfavorable cytogenetics (11 months) ($p = 0.02$). Similarly, OS was improved in patients with +21 with favorable cytogenetics (not reached) or +21 alone (107 months), as compared to +21 with unfavorable cytogenetics (9 months) or +21 with intermediate cytogenetics (8 months) ($p < 0.001$). The differences in TTP and OS were maintained on multivariate analysis ($p = 0.04$ and $p = 0.001$; respectively).

Conclusions—Isolated +21/+21 with favorable aberrations hitherto classified as intermediate-risk cytogenetics may actually behave as a favorable-risk cytogenetics in adult AML patients.

Keywords

trisomy 21; cytogenetic; AML; prognosis; Down's syndrome

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Introduction

Trisomy 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 trisomy 21 in AML stems from the 10–20 fold increased risk of developing acute myeloid leukemia in patients with constitutional +21 or Down's syndrome (DS)[3].

In addition to the frequently identified trisomy 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 may 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 both adult (AML11, AML 12, CALGB 8461, SWOG/ECOG)[10–13] and pediatric (AML12, AML10, NOPHO93, POG 8821, CGS213)[13–18] populations. From these series it can be gleaned that trisomy 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 towards inferior outcomes in AML patients harboring isolated +21 [21,22] [23–25]. Clinically, these patients are characterized for increased expression of lymphocytic markers (namely CD7, CD9 and CD19) in patients with isolated +21 AML suggesting that leukemogenesis in these patients may be occurring at a more primitive or immature phase of hematopoiesis[26–29]. Since +21 aberrations are frequently associated with other karyotypic abnormalities, the predictive and prognostic impact 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.

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 MD Anderson Cancer Center (MDACC) between January 1995 and December 2011. Patients with prior 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 by 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 sub-groups 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 +8 (3 patients), del 20 (1 patient), +4 (1 patient), isodicentric X (IDICX) (1 patient), and +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).

CR was defined by the presence of 5% blasts or less in the bone marrow with greater than $1.0 \times 10^9/L$ neutrophils and greater than $100 \times 10^9/L$ platelets in the peripheral blood. CRp (complete remission with incomplete platelet recovery) included the same criteria as CR, but without recovery of the platelet counts to $100 \times 10^9/L$ or greater. Non-responders (NR) 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.

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 estimates and were compared using the log-rank test. Multivariate comparisons were performed using Cox regression. All *p* values were 2-sided and considered significant if equal to or less than 0.05.

Results

Study group

A total of ninety patients harbored +21 either as an isolated aberration or in combination with other cytogenetic aberrations. The baseline patient characteristics of these patients are shown in table 1. The median age was 59 (range, 18–88) years. All patients received initial therapy for AML at MDACC. Median white blood cell count, peripheral blood blast percentage and bone marrow blast percentage at presentation were $4.6 \times 10^9/L$ (range, 0.6–190), 17% (0–96) and 48% (0–97), respectively. The majority of patients had a FAB M0-M2 (64%) phenotype. Karyotype was +21 alone in 11 patients (12%), +21 with favorable

cytogenetic aberrations in 7 patients (8%), +21 with intermediate aberrations in 7 patients (8%) and +21 with unfavorable aberrations in 65 patients (72%).

Response characteristics

The most frequently administered induction regimen was IA which was used in 36% of the patients, followed by FLU in 24%, CLO and HMT in 11% each, CAT in 10% and MISC in 8% of the patients (table 2). Forty-five (50%) patients achieved a CR, 4 (4%) achieved CRp, 30 (33%) were non-responders (NR) and 11 (13%) died during induction therapy. No significant differences in CR/CRp rate were observed according to the induction regimen ($p = 0.37$) or +21 cytogenetic subgroup ($p = 0.057$). However, there was a trend to improved CR/CRp rates in patients with +21 alone or +21 with favorable cytogenetics as compared to those with +21 with intermediate cytogenetics or +21 with unfavorable cytogenetics (76% versus 50%; $p = 0.057$) (table 3). Of the 49 patients that achieved a CR/CRp, 21 patients (43%) proceeded to allogeneic stem cell transplantation.

Outcomes

Among the 49 patients who achieved a CR, median TTP was 12 (range, 5–19) months (Fig 1A). TTP was significantly longer for patients with +21 alone (not reached) or with +21 with favorable cytogenetics (101 months) as compared to those with +21 with intermediate cytogenetics (2 months) or +21 with unfavorable cytogenetics (11 months) ($p = 0.02$) (Fig 1B). On multivariate COX regression patients with +21 alone maintained an improved TTP as compared to patients with +21 with intermediate cytogenetics or patients with +21 with unfavorable cytogenetics ($p = 0.04$). Covariates assessed included white blood cells, peripheral blasts, previous hematological malignancies, performance status, age, treatment with SCT, and induction therapy (Fig 1C).

Median OS for all patients was 9 (range, 7–11) months (Fig 2A). OS was significantly longer in patients with +21 with favorable cytogenetics (not reached) or +21 alone (107 months), as compared to +21 with unfavorable cytogenetics (9 months) or +21 with intermediate cytogenetics (8 months) ($p < 0.001$) (Fig 2B). On multivariate COX regression, patients with +21 alone maintained an improved OS as compared to patients with +21 with intermediate or patients with +21 with unfavorable cytogenetics ($p = 0.001$). Covariates assessed included white blood cells, peripheral blasts, previous hematological malignancies, performance status, age, treatment with SCT, and induction therapy (Fig 2C).

Discussion

Trisomy 21 is a unique cytogenetic aberration that may occur constitutionally at birth (DS) or may be acquired later in life. Trisomy 21 has a varied clinical impact with distinct biological manifestations in different clinical settings.

In DS +21 is usually “full” implying that the entire chromosome is replicated resulting in a true trisomy. However, other chromosome 21 anomalies have occasionally been identified in individuals with DS including polisomies, ring chromosomes and other trisomy 21 variants[33]. The biological and clinical characteristics of +21 AML in pediatric patients with DS differs significantly from adult patients with acquired +21 AML.

Individuals with DS have a 500-fold increased incidence of acute megakaryoblastic leukemia (FAB class M7) as compared to individuals without DS and the median age of onset is 1.8 years[34]. In patients with DS-associated AML, no chromosomal abnormalities other than +21 are detected in 26% of patients. Thus, majority of the patients have other associated cytogenetic aberrations including trisomy 8 (14%), polysomy 21 (8%) or complex cytogenetic (8%). Deletion 7 and favorable cytogenetic abnormalities [i.e. t(8;21), t(15;17) and inv16] occur concomitantly in only 4% and 2% of patients with DS-associated AML, respectively. Conversely, in our patient population frequently noted chromosome aberrations included inv 16 in 6 patients (7%), +8 in 3 patients (3%), del 7 and abn 11 in 2 patients (2%) each and complex cytogenetics in 65 (72%) patients.

Down's syndrome individuals who develop AML with isolated +21 usually have a favorable prognosis and a 4-year event-free survival of 69%. Induction chemotherapy is usually successful, with complete remissions observed in 95% of cases, but mortality with induction chemotherapy is high with early mortality rates as high as 32%[35]. It has been postulated that patients with chromosome 21 aberrations may have suboptimal metabolism of cytarabine resulting in delayed clearance of the drug with consequent increased toxicity and early mortality from cytarabine-based regimens[36]. In our series isolated +21 was associated with a CR rate of 64% and an early mortality of 9%. In contrast to DS individuals who develop AML, our patients with isolated +21 did not have increased early mortality with cytarabine-containing regimens.

After excluding large epidemiological studies that include AML patients with a multitude of cytogenetic aberrations (table 4), only a few +21 AML specific series could be identified in the literature. In our previous experience, we analyzed 1097 patients with AML or MDS treated at MDACC[37]. Thirty-seven (3.3%) of these patients harbored +21 aberrations: 28 had AML (3% of all AML cases) and 9 had MDS (6 % of all MDS cases). A differential distribution between de novo AML and secondary AML was not identified. In keeping with our current analysis isolated +21 was noted in only 3 of 28 AML cases (10 %). We had previously noted that the most frequently identified concomitant cytogenetic abnormalities in +21 AML/ MDS patients harboring +21 were deletion 5/7 (41% of the patients) and trisomy 8 (24% of the patients). However, in our present analysis +21 AML was most frequently associated with complex cytogenetic aberrations (72% of the patients). We had previously identified FAB M4/M5 AML in 29% of +21 patients, in concordance with published data[38] [39]. In contrast, our current analysis identified FAB M0, M1 and M2 as the main morphological subgroups in +21 AML (64% of our patients) with FAB M4/M5 AML identified in only 10% of the cases.

In our previous study AML patients with isolated +21, receiving induction chemotherapy, had a CR/CRp rate of 50%, with a median CR duration of 22 weeks and a median survival of 34 weeks. When +21 was associated with other concomitant chromosome abnormalities, prognosis was dictated by the latter. In our current analysis we report a CR/CRp rate of 54% with no differences in CR/CRp rates based on cytogenetic subgroups. Interestingly, in our current analysis we noted a longer TTP and improved OS for patients carrying isolated +21 or +21 combined with favorable cytogenetic anomalies. This implies that +21 may in fact be a favorable aberration in adult AML patients, especially when present as a sole aberration or

in concert with favorable cytogenetic changes. This is a novel finding which has hitherto been unreported and may bear clinical significance. Further analysis, particularly genomic expression profiling, may help delineate potential driver mutations in +21 AML identifying possible targets for novel therapeutic agents.

Conclusions

The higher incidence of AML in individuals with DS and the high frequency of +21 in high-risk MDS has sparked interest regarding the etiopathological role of this aberration in myeloid leukemogenesis. Current cytogenetic classification schema classify isolated +21 or +21 with favorable cytogenetic anomalies as an intermediate-risk cytogenetic abnormality in adult patients with non-DS AML, but specific analyses evaluating outcomes in non-DS +21 AML patients are lacking. In our analysis we observed that +21 mostly frequently occurs in combination with unfavorable cytogenetic aberrations including complex karyotypes, -5, -7 or -5/-7 aberrations. However, when present as a sole aberration or in combination with favorable cytogenetic anomalies, +21 is associated with a favorable outcome in AML patients. Thus, isolated +21 and +21 with favorable anomalies which have traditionally been classified as intermediate-risk may actually behave more like favorable -risk cytogenetics in non-DS AML patients.

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Clinical Practice Points

- Children with congenital +21 (Down's syndrome or DS) have a higher incidence of AML.
- Acquired +21 has traditionally been classified as an intermediate risk cytogenetic aberration in adult non-DS AML.
- Acquired +21 frequently occurs in combination with unfavorable cytogenetics (72%) with isolated +21 noted in only 12% of the AML cases in our series.
- In adult +21 AML, remission rates with induction therapy are unaffected by choice of chemotherapy regimen or presence of associated cytogenetic aberrations.
- Isolated +21 or +21 with favorable cytogenetic anomalies hitherto classified as intermediate-risk may in fact behave as favorable-risk cytogenetics in adult AML patients.

Figure 1.

(A) Median time to progression (TTP) for the 49 patients that achieved complete remission after induction therapy (B) Median TTP for the 49 patients that achieved complete remission according to cytogenetic subgroup (C) Median TTP for the 49 patients that achieved complete remission according to cytogenetic subgroup, after multivariate COX regression

Figure 2.

(A) Median overall survival (OS) for all patients (B) Median OS for all patients according to cytogenetic subgroup (C) Median OS for all patients according to cytogenetic subgroup, after multivariate COX regression analysis

Table 1

Patients Characteristics (N = 90)

Characteristic	N (%) / Median [Range]
Age (years)	59 [18–88]
Males	52 (58%)
White	72 (80%)
Black	7 (8%)
Asian	1 (1%)
Hispanic	7 (8%)
Unspecified	3 (3%)
White Blood Cell Count $\times 10^9/L$	4.6 [0.6–190]
Hemoglobin, g/dL	8.6 [3.3–13.4]
Platelets $\times 10^9/L$	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	
+21 alone	11 (12%)
+21 plus favorable	7 (8%)
+21 plus intermediate	7 (8%)
+21 plus unfavorable	65 (72%)
Mutation Analysis	
NPM1	1/25 (4%)
NRAS	4/53 (7%)
CKIT	0/26 (0%)
FLT3	4/49 (8%)

Abbreviations: N, number; +21, trisomy 21

Table 2

Response by induction regimen (N = 90)

Treatment	N (%)	CR	NR	Dead	<i>p</i>
IA	32 (36%)	18 (56%)	9 (28%)	5 (16%)	0.37
FLU	22 (24%)	13 (59%)	7 (32%)	2 (9%)	
CLO	10 (11%)	7 (70%)	2 (20%)	1 (10%)	
CAT	9 (10%)	6 (67%)	3 (33%)	0 (0%)	
HMT	10 (11%)	2 (20%)	7 (70%)	1 (10%)	
MISC	7 (8%)	3 (42%)	2 (29%)	2 (29%)	

Abbreviations: CR, complete remission; NR, non-responders; IA, idarubicin and cytarabine based therapy; FLU, fludarabine based therapy; CLO, clofarabine based therapy; CAT, topotecan based therapy; HMT, hypomethylating agent based therapy; MISC, miscellaneous (including investigational) therapies

Table 3

Response by cytogenetic subgroup (N = 90)

	+21 alone (11)	+21 plus Favourable (6)	+21 plus Intermediate (7)	+21 plus Unfavourable (65)	<i>p</i>
CR (%)	7 (63%)	6 (100%)	2 (29%)	34 (52%)	0.057
NR/dead (%)	4 (37%)	0	5 (71%)	31 (48%)	

Abbreviations: CR, complete remission; NR, no response

Table 4

Incidence of +21 in previously published adult AML analysis.

	AML11 (1065 adults)	CALBG 8461 (1213 adults)	SWOG/ ECOG (609 adults)	AML12 (5876 adults)	AML10 (1612 young)	POG8821 (478 children)	CCG213 (498 children)
Tr21 (%)	26 (2%)	28 (2.3%)	6 (1%)	148 (3%)	45 (3%)	26 (5%)	NA
Tr21al	5	5	NA	NA	NA	7	1
Tr21as	21	23	NA	NA	NA	19	NA

Abbreviations: AML, acute myeloid leukemia; al, alone; as, associated with other cytogenetic aberrations; NA, not available