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# Is translocation (8;21) a "favorable" cytogenetic rearrangement in acute myeloid leukemia?

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**Abstract.** *Twenty-three patients with de novo acute myeloid leukemia (AML) and t(8;21) (q22;q22), including 2 children aged 7 and 14 and 21 adults aged 16 to 68 (median 29), were treated with intensive chemotherapy and 22 (96%) achieved complete remission (CR). Three were allografted in first CR. Median actuarial disease-free interval (DFI) was 17 months in the 22 patients and 14 months when the 3 allografted patients (who did not relapse) were excluded, as compared to 19.5 months in our whole series of AML treated according to the same protocol. After relapse, most patients with t(8;21) reached a second CR, but it was short, except in the 4 patients who were then allografted, and for whom follow-up is insufficient to draw any conclusion. Our findings suggest that, although it is associated with a high CR rate, AML with t (8;21) has a high incidence of relapses, especially in the first year of CR. The term "favorable" cytogenetic rearrangement may be misleading in such cases, and we believe that these patients should receive intensive post-consolidation therapy, possibly including an allograft whenever feasible.*

**Key words :** *Translocation — Acute myeloid leukemia*

## La translocation (8;21) est-elle une anomalie cytogénétique de pronostic favorable dans les leucémies aiguës myéloblastiques ?

**Résumé.** *Vingt-trois patients (dont 2 enfants d'âge 7 et 14 ans, et 21 adultes âgés de 16 à 68 ans, médiane 29), porteurs d'une leucémie aiguë myéloïde (LAM) de novo avec t(8;21) (q22;q22), ont été traités par polychimiothérapie, et 22 (96 %) ont obtenu une rémission complète (RC). 3 d'entre eux ont été allogreffés en 1re RC. La durée médiane de RC est de 17 mois chez les 22 patients et 14 mois si les 3 patients allogreffés sont exclus, contre 19,5 mois dans notre série globale de LAM traitée par le même protocole de chimiothérapie. Après rechute, la plupart des patients avec t(8;21) ont obtenu une 2e RC, mais celle-ci a été courte, sauf chez les 4 patients qui ont alors pu être allogreffés, et chez qui le suivi est insuffisant pour tirer une quelconque conclusion. Ces résultats suggèrent que, bien qu'elles soient associées à un taux élevé de RC, les LAM avec t(8;21) ont une incidence élevée de rechûtes, particulièrement pendant la première année de RC. Le terme d' « anomalie cytogénétique favorable » nous semble trompeur dans le cas des LAM avec t(8;21), et ces patients doivent faire l'objet d'un traitement de consolidation lourd, pouvant éventuellement inclure une allogreffe en 1re RC.*

Cytogenetic results are a well-documented prognostic factor in acute myeloid leukemia (AML) treated with intensive chemotherapy [1,3-16] : abnormalities like partial or complete monosomy for chromosomes 5 or 7 and complex cytogenetic rearrangements have been associated with low complete remission (CR) rates and short CR duration; by contrast, t(8;21) and t(15;17) translocations, and inversion of chromosome 16 (inv (16)) have been correlated with high CR rates and more prolonged median CR duration and are therefore often referred to as "favorable" cytogenetic rearrangements in AML [1, 3-9, 12-16]. In the case of t(8;21), recently published series all found CR rates above 75% in patients treated intensively. Median CR duration, however, was variable. It was certainly prolonged in

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some reports [13, 16], but was relatively short in others [1, 3, 5].

Our preliminary results [4] suggested that, although patients with t(8;21) translocation achieved a high CR rate with intensive chemotherapy, a high incidence of relapses was observed, especially within 12 months of CR achievement. At the time of this report, however, quite a few of those patients had a relatively short follow-up and definite conclusions could not be made. We have therefore updated our results, also adding a few patients, all diagnosed at least 16 months before the closing date of the present study.

## Patients and methods

Between January 1981 and September 1988, cytogenetic analysis was performed at diagnosis in 315 patients with de novo AML (according to FAB criteria) [2], excluding patients with AML secondary to chemotherapy, radiotherapy or occupational exposure. In 16 of these, no or insufficient mitoses were obtained. Twenty-three of the 299 patients who had adequate mitoses (7.6%) showed a t(8;21) (q22;q22) translocation, and are the subject of this report. Closing date of the study was January 1990, 16 months after the last patient's inclusion.

All 23 patients received intensive chemotherapy with protocols OI AM 81 or OI AM 86 (Institut de Recherche sur les Maladies du Sang, Hôpital St Louis, Paris), including a zorubicin (200 mg/m$^2$/d $d_{1\ to\ 4}$) + Ara C (200 mg/m$^2$/d $d_{1\ to\ 7}$) induction regime, followed, in responding patients, by consolidation and maintenance courses according to protocol randomization [10]. Three patients were allografted (from HLA-identical siblings) in first CR, 2, 2 and 3 months from CR. Two patients were also autografted in first CR, 5 months after CR.

Cytogenetic analysis was performed on bone marrow short term 24 h culture; chromosomes were identified using R and/or G banding (RHG and GTG) and classified according to the ISCN [6].

Survival and disease-free interval (DFI) curves were constructed using the Kaplan Meier method. The following factors were analyzed for their prognostic value on DFI : age, sex, leukocytes, neutrophils, presence of clonal abnormalities in addition to t(8;21). Comparisons were made using the log rank test.

## Results

### *Clinical and laboratory features at diagnosis*

These are detailed in Table 1. There were 2 children (aged 7 and 14) and 21 adults aged 16 to 68 (median 29). Extramedullary leukemia consisted of splenomegaly (2 cases) and peripheral lymphadenopathy (1 case). Leukocytosis ranged from 1.7 to 86×10$^9$/l (median 14). Translocation (8;21) (q22;q22) was associated with another clonal abnormality in two-thirds of the patients.

### *Therapeutic results*

Twenty-two patients (96%) reached CR. The remaining patient died of sepsis, during the period of aplasia. Twenty-one of the CR were obtained after one induction course and the remaining CR only after a second zorubicin-Ara C regimen. One patient died in CR after 7 months, during the period of aplasia which followed a consolidation course. Thirteen patients relapsed, 9 within one year of CR achievement and 4 after one year (14, 17, 20 and 29 months, respectively). Eight patients remained in CR after $14^+$ to $75^+$ months (more than 24 months in 4 cases) including the 3 patients allografted in first CR and 1 of the 2 patients autografted in first CR (Fig. 1). Median actuarial DFI was 17 months in all complete remitters and 14 months in the 19 complete remitters who were allografted in first CR (Fig. 1).

Ten of the patients who relapsed were retreated: 1 was allografted with an HLA-identical sibling in "early" relapse; 9 received combination chemotherapy, including high-dose Ara C - mitoxanthrone (6 patients) and zorubicin - Ara C - cyclophosphamide (3 patients), and 8 achieved a second CR, of whom 3 were rapidly allografted. All 4 patients allografted after relapse were surviving after $2^+$, $3^+$, $4^+$ and $25^+$ months. All the other patients with relapse died, after 1 to 19 months (median 8). None of the parameters listed in Table 1 had any prognostic value on DFI (data not shown).

**Table 1.** Clinical and laboratory features at diagnosis

| | |
|---|---|
| *Age* | |
| Children | 7 and 14 |
| Adults | median 29 (range 16-68) |
| *Sex* | |
| F | 6 |
| M | 17 |
| *Extramedullary leukemia* | 3 |
| *Leukocytes* ($10^9$/l): median 14 (range 1.7-86) | |
| <10 | 9 |
| >10 | 14 |
| *Neutrophils* ($10^9$/l: median 1.8 (range 0.4-44) | |
| <2 | 13 |
| >2 | 10 |
| *FAB* | |
| $M_1$ | 2 |
| $M_2$ | 21 |
| *Karyotype* | |
| t(8;21) alone | 8 |
| t(8;21) and others | 15 |
| • −Y | 9 |
| • −X | 2 |
| • deletion 9q | 3 |
| • trisomy 4 | 1 |

## Discussion

Our findings confirm several of the characteristics previously found in AML with t(8;21) (q22;q22): predominance in younger patients and in males, and $M_2$ FAB subtype in most if not all cases [3-9, 12-16]. As in

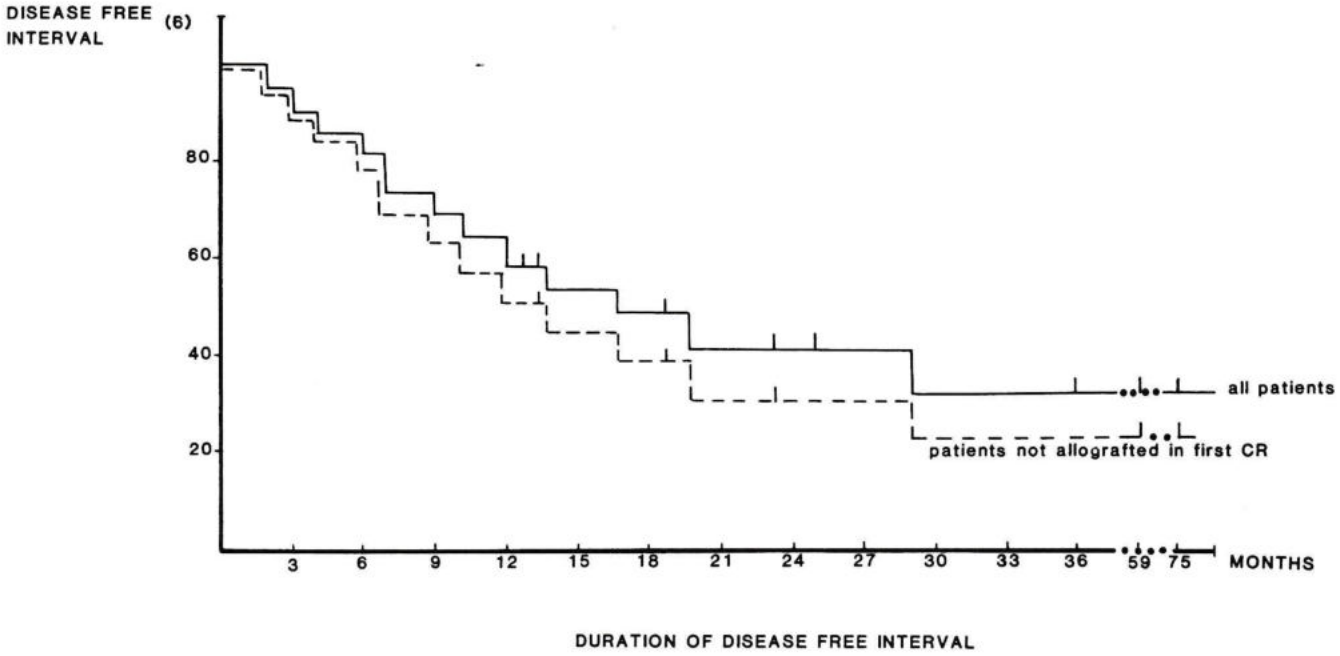


**Fig. 1.** Actuarial disease-free interval in patients who reached CR (vertical bars : patients still at risk)

previously reported series, we found a high CR rate in patients with t(8;21): 96%, as compared to 82% to 93% in the literature (Table 2). This was slightly higher than in patients belonging to other cytogenetic categories (except perhaps in patients with inv (16), both in our experience (overall CR rate of 76% in AML) (4, updated results), and in other reports [3-9, 12, 13, 15, 16].

We found, however, a high incidence of relapses in our patients, especially during the first year following CR achievement. Median actuarial DFI was 17 months and 14 months, respectively, in all patients and in patients who where not allografted in first CR, as compared to 19.5 months in our overall population of AML [4, updated results]. In addition, survival was short after relapse in patients who could not be allografted. Those results are in agreement with the results reported by Berger et al in patients treated with the same chemotherapy protocols as our own (Table 2). The International Workshop also reported a short median CR duration, but this was a multicenter series which included patients diagnosed between 1980 and 1982, many of whom had received less intensive treatment protocols (Table 2). Accordingly, median survival was only 20 months in the report of Trujillo et al [15], but in patients diagnosed prior to 1976, who received relatively moderate chemotherapy. Patients with t(8;21), in this report, had a better outcome than the average AML. In 3 other reports [8, 13, 16], including one pediatric series [8], t(8;21) was associated with prolonged median remission duration (Table 1). Finally, in one series where t(8;21) was regarded as "favorable", the median duration of CR was in fact relatively short, not exceeding 16 to 17 months [6, 7, 11].

Our findings therefore suggest than the term "favorable" may be misleading in the case of AML with t(8;21). Those patients, in fact, especially because they are generally young, should receive intensive post-induction therapy like other AML variants. The choice between the different types of intensive post-induction approaches (high-dose chemotherapy, autologous or

**Table 2.** Outcome of AML with t(8;21). Major reported series

| | No Patients | CR rate (%) | Median CR duration (months) | Median survival (months) |
|---|---|---|---|---|
| Arthur et al. (1) FIWCL (5) | 25 | 84 | 8 | 14 |
| Berger et al (3) | 43 | 92.6 | NR | 15.3* |
| Kalwinsky+et al (7) | 14 | 86 | 24 | NR |
| Keating et al (8) | 27 | 93 | 16.7 | NR |
| Schiffer et al (11) | 13 | 82 | 26.7 | NR |
| Swirsky et al (12) | 33 | 88 | 18 | 24 |
| Trujillo et al (13) | 32 | 84 | NR | 20 |
| Yunis et al (14) | 9 | NR | NR | NA |

*: in patients who achieved CR
NR: not reported
NA: not attained
+: included children only

allogenic bone marrow transplantation) remains controversial in AML with t(8;21), however, as in other AML. For instance allografting, when possible, may be performed in first CR, but may also only be considered after relapse, given the high rate of second CR we obtained then with salvage chemotherapy.

## References


1. Arthur D, Berger R, Colomb H, Swaasbury G, Reeves B, Van den Berghe H, de La Chapelle A, Garson O, Alagemeier A, Kaneko Y, Rowley J (1989) The clinical significance of karyotype in acute myelogenous leukemia. Cancer Genet Cytogenet 40 : 203-16
2. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Gralnick H, Galton D, Sultan C (1976) Proposals for the classification of acute leukaemias. Br J Haematol 33 : 451-458
3. Berger R, Bernheim A, Ochoa Noguera ME, Daniel MT, Valensi F, Sigaux F, Flandrin G, Boiron M (1987a) Prognostic significance of chromosomal abnormalities in acute nonlymphocytic leukemia : a study of 343 patients. Cancer Genet Cytogenet 28 : 293-299
4. Fenaux P, Preudhomme C, Laï JL, Morel P, Beuscart R, Bauters F (1989) Cytogenetics and their prognostic value in de novo acute myloid leukaemia : a report on 283 cases. Br J Haematol 73 : 61-67
5. Fourth International Workshop on Chromosomes in Leukemia 1982 (1984) Clinical significance of chromosomal abnormalities in acute non-lymphoblastic leukemia. Cancer Genet Cytogenetic 11 : 332-350
6. Groupe Français de Cytogénétique Hématologique (1990) Acute myelogenous leukemia with an 8;21 translocation : a report on 148 cases from the Groupe Français de Cytogénétique Hématologique. Cancer Genet Cytogenet 44 : 169
7. ISCN (1985) An international system for human cytogenetics nomenclature. In : Harden DG, Klinger HP (eds). Birth Defects : original article series, Vol. 21, No 1, New York, NY, March of Dimes Birth Defects Fondation, 1985
8. Kalminsky D, Raimondi S, Schell M, Mino J, Santana V, Behm F, Dahl G, Williams D (1990) Prognostic importance of cytogenetic subgroups in de novo pediatric acute non-lymphocytic leudemia. J Clin Onc 8 : 75-83
9. Keating MJ, Smith TL, Kantarjian H, Cork A, Walters R, Trijille JM, Mc Credie K, Gehan E, Freireich E (1988) Cytogenetic pattern in acute myelogenous leukemia : a major reproducible determinant of outcome. Leukaemia 2 : 403-412
10. Marty M, Lepage E, Guy H, Bordessoule D, Guilhot F (1987) Remission duration in ANLL : a multicentric study of prognostic factors in 461 patients. 4th International Symposium on Therapy of Acute Leukemias, Rome, p 258
11. O'Brien J (1989) Association of granulocytosis with poor prognosis in patients with acute myelogenous leukemia and translocation of chromosomes 8 and 21. J Clin Oncol 7 : 1081
12. Samuels B, Larson R, Le Beau M, Daly K, Bitter M, Vardiman J, Barker C, Rowley J, Colomb H (1988) Specific chromosomal abnormalities in acute nonlymphocytic leukemia correlate with drug susceptibility in vitro. Leukaemia 2 : 79-83
13. Schiffer CA, Lee EJ, Tomiyasu T, Wiernik PH, Testa JR (1989) Prognostic impact of cytogenetic abnormalities in patients with de novo acute non-lymphocytic leukemia. Blood 73 : 263-270
14. Swirsky D, Li Y, Matthews J, Flemans R, Rees J, Hayhoe F (1984) 8;21 translocation in acute granulocytic leukaemia : cytological, cytochemical and clinical features. Br J Haematol 56 : 199-213
15. Trujillo J, Cork A, Ahearn M, Youness E, Mc Credie K (1979) Hematologic and cytological characterization of (8;21) translocation in acute granulocytic leukemia. Blood 53 : 695-706
16. Yunis JJ, Lobell M, Arnesen MA, Oken M, Mayer M, Rydell R, Brunning R (1988) Refined chromosome study helps define prognostic subgroups in most patients with primary myelodysplastic syndrome and acute myelogenous leukaemia. Br J Haematol 68 : 189-194


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