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Trisomy 8 as the sole chromosomal aberration in acute myeloid leukemia and myelodysplastic syndromes

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Keywords: Trisomy 8; Acute myeloid leukemia; Myelodysplastic syndrome; Sole chromosomal aberration

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CT8M, constitutional trisomy 8 mosaicism; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndromes; RA, refractory anemia; RAEB, refractory anemia with excess of blasts; SCT, stem cell transplantation; SNP, single nucleotide polymorphism, UPD, uniparental disomy.

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Abstract

Trisomy 8 as the sole abnormality is the most common karyotypic finding in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), occurring in approximately 5% and 10% of the cytogenetically abnormal cases, respectively. However, despite the high frequency of +8, much remains to be elucidated as regards its epidemiology, etiology, clinical impact, association with other chromosomal abnormalities, cell of origin, and functional and pathogenetic consequences. Here, we summarize and review these various aspects of trisomy 8, focusing on AMLs and MDS harboring this abnormality as a single change.

1. Introduction

Already in the late 1950s and early 1960s, cytogenetic studies of acute myeloid leukemias (AMLs) revealed that many of them were aneuploid, often with hyperdiploid modal numbers at 47 or 48 [1-3]. Although it was not possible to characterize further the chromosomal abnormality patterns in this pre-banding era, one aberration seemed quite common, namely a "group C-trisomy" [4,5]. When the various chromosome banding techniques were introduced in the 1970s, it was soon realized that the extra C chromosome in AML, as well as in myelodysplastic syndromes (MDS), in the vast majority of the cases represented a trisomy 8 [6-8]. To date, close to 500 AMLs and 400 MDS with this abnormality as the sole chromosomal anomaly have been published [9].

In spite of the quite substantial number of trisomy 8-positive cases reported, many issues regarding the epidemiology, etiology, morphologic, immunophenotypic, and prognostic features, association with other genetic abnormalities, cell of origin, and the pathogenetic impact of +8 still needs to be clarified, as will be illustrated in the present review of AML and MDS with trisomy 8 as the sole chromosomal change.

2. Epidemiology

A survey of cytogenetically abnormal AML and MDS cases reported in the literature [9] shows that trisomy 8 is present in 16 – 17% of these disorders and that it is the sole change in 6% and 11% of the AMLs and MDS, respectively (Tables 1 and 2); frequencies agreeing well with published series of karyotypically characterized AMLs and MDS [10-14]. In fact, +8 is, on the whole, the most common chromosomal change in AML and the second, next to monosomy 7, in MDS; as the sole aberration, it is the most frequent one in both these disorders. Isolated trisomy 8 is also quite common in chronic myeloproliferative disorders, such as polycythemia vera and myelofibrosis [15]. Hence, this abnormality is strongly

associated with myeloid malignancies. However, it should be stressed that +8 as the single change is not specific for such disorders. In fact, trisomy 8 occurs in a wide spectrum of different neoplastic disorders. For example, close to 50 cases of acute lymphoblastic leukemias (ALL), many of which of T-cell lineage, with +8 as the single anomaly have been published, and some solid tumor types/lesions, in particular desmoid tumors and Dupuytren's contracture, are also characterized by this abnormality [16-18]. Trisomy 8 is also common together with other chromosomal aberrations in a large number of tumor types, such as colon, breast, and head and neck cancer [19-21], Wilms tumor [22], and hepatoblastoma [23]. Furthermore, +8 is a common secondary change in several neoplastic disorders with characteristic primary translocations, e.g., chronic myeloid leukemia (CML) with t(9;22)(q34;q11), myxoid liposarcomas with t(12;16)(q13;p11), clear cell sarcomas with t(12;22)(q13;q12), synovial sarcomas with t(X;18)(p11;q11), and Ewing tumors with t(11;22)(q24;q12) [24-28]. Thus, +8 seems to play an important role neoplasia, seemingly irrespective of the histogenetic derivation of the neoplasm.

We have previously reported that +8 as the sole change does not display any gender-related frequency differences in AML and MDS [29]. An updated database search [9] on isolated trisomy 8 reveals that it is seen in 6.0% and 6.8% of karyotypically abnormal AMLs in women and men, respectively. However, a significantly higher frequency in males (12% versus 8.9%; $P<0.05$; chi-square test) is found in MDS, in agreement with a previous study by Pedersen [30]. Furthermore, there is a clear-cut impact of age on the incidence of trisomy 8 as a sole change in AML, i.e., it increases with age [29,31]. In MDS, on the other hand, the frequencies of +8 do not vary significantly among the various age groups (Table 3). The incidences of trisomy 8 as the single anomaly in AML also differ significantly among the continents, from approximately 4% in Asia to more than 16% in Oceania, whereas there is no

significant geographic frequency heterogeneity in MDS, varying from approximately 7% in Latin America to 12% in Europe (Table 4).

Taken together, although some of the observed significant differences mentioned above may be fortuitous, the available data – revealing gender-, age-, and geography-related frequency differences – have etiological ramifications, suggesting that one or several intrinsic and/or extrinsic factors play a role in the origin and formation of +8.

3. Etiology

Apart from the fact that trisomy 8 most likely arises through nondisjunction, little is known about the constitutional/environmental risk factors for, this chromosome abnormality.

It is generally accepted that +8 in AML and MDS is an acquired abnormality, being present in the neoplastic cells only. However, trisomy 8 may also be constitutional, occurring as a mosaicism (CT8M) in approximately 0.1% of all recognized pregnancies [32]. Typically, CT8M is the consequence of a postzygotic nondisjunction, and as expected for a gain arising through this mechanism, there is no preferential parental origin of the extra chromosome [33,34]. CT8M is associated with mild to moderate mental retardation, facial dysmorphic features, bone and joint abnormalities, and cardiovascular and urogenital malformations; however, some present with an apparently normal phenotype, including normal intelligence [35]. Individuals with CT8M have an increased risk for developing neoplastic disorders, in particular myeloid malignancies which seem to occur in approximately 5% of the patients [36-39]. This – together with the fact that CT8M may be associated with a normal phenotype – has led several investigators to suggest that +8 in some AMLs and MDS may be constitutional [36,38,40,41]. In fact, Maserati et al. [42] reported that two of fourteen trisomy 8-positive myeloid malignancies were previously undetected CT8M. However, it should be

stressed that although isolated +8 in leukemia hence may be constitutional in some instances, this rather high frequency remains to be confirmed.

In contrast to some other abnormalities, such as whole or partial losses of chromosomes 5 and 7 and rearrangements of 11q23/*MLL*, trisomy 8 in AML and MDS is not associated with prior treatment with radiotherapy, alkylating agents, or drugs targeting DNA topoisomerase II. In fact, +8 as the sole change is significantly more frequent in de novo AML and MDS than in treatment-related cases [29,43]. In t(9;22)(q34;q11)-positive CML, on the other hand, trisomy 8-harboring clones, of unknown clinical and pathogenetic importance and without the t(9;22), frequently arise after interferon-alpha and – in particular – imatinib treatment [44-46]. It is presently unclear whether interferon-alpha or imatinib merely allow a pre-existing clone to expand or whether they have a direct effect the nondisjunction event [46].

Next to nothing is known about environmental risk factors for trisomy 8-positive AMLs and MDS. However, previous occupational exposure to organic solvents, mainly benzene, has been suggested to increase the risk for AML with +8 as the sole change [47,48]. Further support for an etiologic role of benzene has come from in vitro studies, using interphase fluorescence in situ hybridization (FISH), showing that exposing peripheral blood cells or CD34+ cells from chord blood to metabolites of benzene, e.g., hydroquinone and benzenetriol, results in aneuploidy of chromosome 8 [49-51]. This was, however, not confirmed in similar experiments on CD34+ bone marrow cells [52]. In vivo analyses, by the use of interphase FISH, of lymphocytes from benzene-exposed workers have also identified increased frequencies of trisomy 8, which in one study was associated with polymorphisms in genes encoding benzene-metabolizing enzymes [53,54]. Thus, benzene exposure does seem to be a bona fide risk factor for +8. Smoking has also been associated with trisomy 8-positive AML [55,56], although this could not be confirmed in a more recent study [57]. Further

investigations addressing this issue are hence needed before any firm conclusions can be drawn.

4. Morphologic, immunophenotypic, and prognostic features

Although +8 as the sole change may be found in all morphologic subgroups of AML, it has been reported that it is particularly frequent in M1, M2, M4, and M5, with a higher incidence in M5a than in M5b [12,13,29,58-63]. An updated database search [9] reveals that the frequencies of +8 as the sole change vary significantly among the different morphologic subtypes, being most common in M5, albeit with identical incidences in the M5a and M5b subgroups (Table 1). In MDS, isolated trisomy 8 has been suggested to occur predominantly in refractory anemia (RA), chronic myelomonocytic leukemia (CMML), and refractory anemia with excess of blasts (RAEB) [14,29,64-66]. However, no statistically significant frequency differences among the various MDS morphologic subtypes were observed in the present database search (Table 2).

AMLs with +8 do not seem to display any specific immunophenotypic features [67], although it should be stressed that very few investigations have addressed this issue. In fact, only two larger studies specifically focusing on immunophenotypic findings in AMLs with trisomy 8 have been reported to date; to the best of our knowledge no such investigations have been performed on MDS with +8. Casasnovas et al. [68] showed that trisomy 8-positive AMLs often express CD13 and CD33 and that this karyotypic subset differs from other cytogenetically abnormal AMLs by having a lower frequency of CD34 expression, being similar to AMLs with a normal karyotype, and it has been reported that +8 is significantly associated with expression of CD36, a monocytic marker [69]. Further studies are definitely needed in order to confirm and extend these findings.

Surprisingly little is known about the prognostic impact of trisomy 8 as the sole change in AML and MDS considering its high frequency in these disorders. This is to a large extent due to the fact that many studies have combined cases with isolated +8 with those having additional abnormalities, precluding any clear-cut conclusions as regards the importance of trisomy 8 as the sole change. In Table 5, the basic clinical characteristics reported in larger series of AMLs with +8 as the single anomaly are summarized. As seen, it is quite obvious that trisomy 8 does not confer a particularly favorable prognosis in AML. However, it is less clear whether it is associated with an intermediate [13,60,71,72,76] or a poor prognosis [12,61,62,65,75]. The reasons for the variable clinical outcome in different studies are most likely manifold, including differences in patient characteristics and in treatment protocols. AMLs with +8 as the sole anomaly are generally included in the “intermediate cytogenetic group” in treatment protocols, to a large extent based on the findings of the MRC AML 10 trial [72]. However, it should be emphasized that it has been reported that trisomy 8-positive AMLs are not responsive to cytarabine-based therapy; in fact, it has been suggested that stem cell transplantation (SCT) in first remission may have a beneficial effect and that SCT thus should be considered, at least in younger patients [12,61,62]. Our knowledge about the impact of +8 as the sole change in MDS is even more limited (Table 6). As in AML, it is usually included in the intermediate prognosis group [10,79]. However, most studies have reported quite a high incidence (38 – 62%) of AML transformation (Table 6). Taken together, although +8 as the sole change in AML and MDS often is considered to confer an intermediate prognosis, several investigations suggest that these cases may have a worse outcome than other cytogenetic subtypes within the clinically very heterogeneous intermediate prognosis group. It is in this context noteworthy that a recent review of AML and MDS with tetrasomy, pentasomy, or hexasomy 8 revealed that the presence of polysomy 8 constitutes an adverse prognostic feature [80].

5. Trisomy 8 associated with other chromosomal abnormalities

In AML, trisomy 8 also occurs in association with other abnormalities in 10% of the cytogenetically abnormal cases (Table 1). In fact, trisomy 8 is quite common as a secondary change to a large number of primary AML-associated translocations and inversions [81], being particularly prevalent in cases with t(7;12), t(9;11), and t(1;11) (Table 7). Furthermore, it is the most common secondary change in AMLs with t(9;11)(p21;q23), t(9;22)(q34;q11), t(11;19)(q23;p13), and t(15;17)(q22;q21), and the second most frequent in cases with t(6;11)(q27;q23), t(7;12)(q36;p13), and inv(16)(p13q22) [82-86]. Even though the presence of a secondary trisomy 8 does not seem to have a prognostic impact, at least not in the favorable prognosis group comprised of t(8;21)(q22;q22), t(15;17)(q22;q21), and inv(16)(p13q22) [12,13,60,72,87-89], its high frequency as an additional change strongly suggests that it does provide a selective advantage to the AML clone in which it arises. In fact, it has been reported that AMLs and MDS with +8 have a higher proportion of this abnormality in dividing bone marrow cells than in non-dividing cells, as ascertained by interphase FISH, indicating that it confers a proliferative advantage, at least in vitro [90]; however, such a discrepancy can also be due to suboptimal FISH hybridization as well as to admixture of non-diving nonneoplastic cells [91]. In MDS, trisomy 8 occurs together with other abnormalities in approximately 5% of the cases, being particularly common in association with der(1;7)(q10;p10), +19, and +21 (Tables 2 and 8). The clinical impact of an additional +8 in MDS is presently unknown.

6. Cell of origin

During the past decade, cancer stem cells, the existence of which was first proposed more than 40 years ago, have received much attention [92-94]. It is now generally accepted, or at least widely believed, that hematologic malignancies are sustained by leukemic stem cells,

capable of both initiating and maintaining the disease. Apart from functional studies, FISH analyses of neoplasia-associated genetic abnormalities in morphologically or phenotypically defined cell populations have been instrumental in identifying the cell lineages affected in AML and MDS, providing circumstantial evidence for candidate leukemia stem cells [95-102].

Several studies of AMLs with +8 as the sole change have used this abnormality as a marker for elucidating which cells are involved in the neoplastic clone. Before the advent of FISH, simultaneous karyotypic and phenotypic analyses of the same metaphases revealed that the granulocytic-monocytic lineage, occasionally also the erythrocytic lineage, was involved in trisomy 8-harboring AMLs irrespective of the morphologic subtype, suggesting that the leukemic clone was derived from a multipotent stem cell, although the cell of origin seemed to vary depending on the number of lineages involved [103-105]. Subsequently, interphase FISH analyses on sorted cells showed that +8 was present not only in CD34+CD38-CD33- cells but also in erythroid and megakaryocytic cells as well as in B and T lymphocytes, strongly suggesting that AMLs with trisomy 8 arise in an early hematopoietic stem cell [98,99,106]. It should be noted that the involvement of the stem cell compartment is not specific for +8. In fact, there is evidence that all AMLs, with the exception of acute promyelocytic leukemia [107,108], arise in hematopoietic stem cells [94].

The cell in which trisomy 8 occurs as the single anomaly in MDS has also been analyzed in some detail, but the conclusions drawn have been somewhat disparate. Several early FISH studies of MDS cases of all subtypes showed that this abnormality was present in the myeloid compartment, often including granulocytes, monocytes, megakaryocytes, and erythroblasts, but not in lymphocytes and plasma cells, i.e., it was restricted to the myeloid lineage. It was thus concluded that trisomy 8 in MDS does not arise in a multipotent stem cell and that, considering variable involvement of the various myeloid subpopulations, it occurred

at different levels in the hematopoietic hierarchy [95,96,100,105,109-115]. However, these findings did not exclude the possibility of an additional chromosome 8 arising in a multipotent stem cell but at the same time suppressing differentiation of the lymphoid lineage. In fact, +8 has been identified in a low frequency of lymphoid cells in MDS, and a few trisomy 8-harboring MDS cases have been reported to transform to ALL with +8 [116-118], indicating involvement of an early pluripotent stem cell. More recently, it was reported that the hematopoietic stem cell pool (CD34+CD38-Thy-1+ cells) harbored +8, although a sizeable fraction still was disomic for this chromosome [101]. Interestingly, the cells with disomy 8 were functionally abnormal, suggesting that they were nevertheless part of the MDS clone and that +8 was a secondary event in the MDS development. Further support for this was obtained in MDS cases with trisomy 8 in addition to 5q-, in which the latter aberration was shown to precede the extra chromosome 8 [101].

7. Pathogenetic impact of trisomy 8

Although several attempts to elucidate the pathogenetic impact of +8 have been made, the functional and molecular genetic outcome of this abnormality remains elusive. Possible mechanisms that may be involved include global gene expression changes, resulting from the gene dosage effect generated by the trisomy, deregulation of imprinted loci, and duplication of rearranged or mutated genes present in the extra chromosome 8. The pros and cons of these various possibilities are reviewed below.

7.1. Gene dosage effect?

It has been suggested that the effect of trisomy 8 can be reduced to gain, and supposedly overexpression, of the *MYC* gene located at 8q24 [119-121]. However, considering that chromosome 8 contains approximately 800 genes [122] we deem it too simplistic to ascribe

the functionally essential consequence of +8 to one extra copy of one single gene. The perhaps strongest argument against *MYC* as a target of +8 is the fact that it is down-regulated in trisomy 8-positive AMLs as ascertained by microarray analysis [123]. Furthermore, it has been shown that *MYC* is not even up-regulated when it is highly amplified in AMLs and MDS with *MYC*-containing dmin [124]. In addition, Mertens et al [125] cytogenetically mapped the chromosome 8 gains present in close to 2,000 cases of myeloid malignant disorders and showed that such imbalances almost always occurred in the form of a trisomy and that they could not be reduced to a single chromosome band, concluding that the pathogenetic effect of trisomy 8 was unlikely to be upregulation of only one gene on this chromosome. Instead, duplication of chromosome 8 seems to be associated with global gene expression changes, as revealed by microarray analyses of AMLs with isolated trisomy 8.

To date, four microarray studies of AMLs with +8 as the sole aberration have been reported [123,126-128]. Virtaneva et al [123] specifically compared trisomy 8-harboring AMLs with cases with a normal karyotype, whereas the other groups included various additional cytogenetic subgroups in the investigations. Interestingly, unsupervised analyses did not reveal any clustering of AMLs with +8 [123,126,127], suggesting that there is no strong gene expression signature associated with gain of chromosome 8. However, characteristic expression patterns were identified in two of three supervised analyses, i.e., investigations including only pre-selected genes [126-128]. Taken together, the available data indicate that the +8 subgroup has a heterogeneous gene expression profile compared with AMLs with well-known primary translocations and inversions. In line with this, different genes have been shown to be up- or down-regulated in the various investigations. Obviously, this discrepancy could be due to the fact that different array platforms were used in the different studies, but it could also reflect an underlying heterogeneity of trisomy 8-positive AMLs. A general overexpression of genes on chromosome 8 was noted in three of the

analyses, corresponding to 1.32 [127], 1.27 [123], and 1.13 [128] times the level in AMLs with a normal karyotype. However, it should be noted that a substantial proportion of the chromosome 8 genes was not up-regulated, clearly demonstrating that gain of chromosome 8 does not automatically confer a higher expression of the genes located at this chromosome. The biologic function of the differentially expressed genes has not been investigated in most studies, but Virtaneva et al [123] found an underexpression of genes involved in apoptosis.

As regards MDS with isolated +8, only one microarray analysis has been reported. Chen et al [129] compared the gene expression profiles of purified CD34-positive cells from MDS cases with trisomy 8 with those from monosomy 7 cases. They found a specific expression signature, but in contrast to the findings in AML no general up-regulation of genes mapping to chromosome 8 was found.

In conclusion, more expression studies are clearly needed in order to obtain a clear picture of which genes are de-regulated as a consequence of trisomy 8 in AML and MDS.

7.2. Imprinting?

Although no larger studies have specifically addressed the parental origin of the gained chromosome 8 in AML and MDS, there is some information available from a handful of CT8M patients with these disorders and from a few families with a high incidence of AML and MDS. In total, four cases with maternal origin and two with paternal origin of the +8 have been reported [38,130-132], indicating that there is no preferential duplication of maternally or paternally inherited alleles. Taken together with the facts that no genes on chromosome 8 have been clearly shown to be imprinted, that no AMLs with acquired segmental uniparental disomy (UPD) involving chromosome 8 loci have been reported, and that constitutional UPD for chromosome 8 seems to be associated with a normal phenotype [133-138], it does seem

highly unlikely that imprinting effects related to the parental origin of the gained chromosome is of pathogenetic importance in trisomy 8-positive AMLs and MDS.

7.3. Duplication of mutated/rearranged chromosome 8 genes?

Some trisomies have been associated with mutations of genes located at the chromosomes involved, e.g., duplications of mutated *KIT*, *MET*, and *JAK2* alleles as a consequence of trisomy 4 in t(8;21)(q22;q22)-positive AMLs [139], trisomy 7 in hereditary papillary renal carcinoma [140], and trisomy 9 in polycythemia vera [141], respectively. In addition, a nonrandom duplication of the mouse chromosome carrying a mutated *Hras1* gene has been reported in studies of induced mouse squamous cell carcinomas [142]. Furthermore, trisomy 11 as the sole change in AML has been correlated with a partial tandem duplication of the *MLL* gene [143]; however, only one chromosome 11 contains the mutated allele in these cases [144], showing that there is no clear-cut association between trisomies and copies of mutated genes.

As regards trisomy 8, only a few studies have looked for cryptic rearrangements or mutations of genes on this chromosome. Diaz et al. [145] investigated, using Southern blot analysis, the *MYC* and *MOS* genes in six MDS cases with isolated trisomy 8 and four AMLs with +8 in addition to other changes. Germline fragments were found in all cases, except in one MDS in which a rearranged *MYC* fragment – not further investigated – was detected. They concluded that trisomy 8 generally is not associated with rearrangements of these two genes. More recently, Raghavan et al. [138], applying the single nucleotide polymorphism (SNP) array technology, found no evidence for segmental UPDs on chromosome 8 in two AMLs with trisomy 8. Furthermore, Heller et al. [146], who used multicolor banding specifically to study chromosome 8 in eight AML and MDS cases with this trisomy as the sole aberration, reported that all three homologues were normal. Finally, we found no cryptic

abnormalities using FISH with partial chromosome paint and subtelomeric probes for 8p and 8q as well as specific probes for the leukemia-associated *FGFR1*, *MYST3* (*MOZ*), *RUNX1T1* (*ETO*), and *MYC* genes in 12 AML and MDS cases with +8 [147]. Thus, the available data, albeit limited, do not support that the pathogenetic outcome of trisomy 8 is related to the presence, and subsequent duplication, of mutated or rearranged genes on this chromosome. This is perhaps not unexpected considering the development of myeloid malignancies in patients with CT8M (see above). The fact that the trisomy 8 is present at birth but that the leukemia in these patients occurs later in life strongly suggests that additional abnormalities would have to occur after the trisomy.

Another possibility, admittedly a farfetched one, is that all three copies of chromosome 8 are structurally rearranged in cases with +8, i.e., the seemingly normal homologues are in fact a balanced t(8;8) – with cytogenetically identical, but molecularly distinct, breakpoints – and an additional der(8)t(8;8). If so, the functional outcome of such a “trisomy 8” could be a fusion gene with gain of either the critical or non-critical derivate, the latter being a frequent finding in AMLs and other neoplastic disorders characterized by primary translocations [148]. There is to date no evidence in favor of this hypothesis, but the cytogenetically cryptic t(12;21)(p13;q22) [*ETV6/RUNX1* fusion] in childhood ALL may be used as an example of this possibility. Trisomy 21 is one of the most common secondary abnormalities in t(12;21)-positive ALLs, and although all three chromosomes 21 are cytogenetically normal in these cases the extra copy is the result of duplication of either the normal chromosome 21 or the der(21)t(12;21) [149-151]. If trisomy 8 in fact represents a gain of a der(8)t(8;8) then it is clearly a secondary change to a balanced t(8;8). Thus, disomic cells would still be a part of the neoplastic clone, something that could explain the findings reported by Nilsson et al. [101] as regards the stem cell involvement in MDS (see above).

8 Trisomy 8 is not sufficient for leukemogenesis

Trisomy 8 is an important early event, but several lines of evidence quite strongly indicate that it is not sufficient for leukemogenesis. First, although individuals with CT8M have an increased risk of myeloid malignancies, only a minority develop AML or MDS, with a latency of several years [37,39,42]. Second, several cytogenetic as well as clonality studies of trisomy 8-positive MDS cases have indicated that +8 is not the primary event in the malignant transformation, i.e., also the disomic cells have been either shown, or strongly suggested, to be part of the malignant clone [101,110,113,152,153]. Third, Schoch et al. [128] reported that that the discriminating gene expression pattern of AMLs with isolated trisomy 8 did not depend on the upregulation of chromosome 8 genes alone, concluding that additional genetic changes could be present. Fourth, the fact that +8 is a common secondary aberration in AML and MDS (Tables 7 and 8) and often one of the abnormal clones in cytogenetically polyclonal hematologic malignancies [9,81,154,155] indicates that it may be involved in the evolution of AML/MDS rather than in the initial leukemic transformation. Fifth, there is, as yet, no evidence for an increased risk of MDS in CML patients with trisomy 8-positive, t(9;22)-negative clones emerging after treatment with imatinib [46]. Finally, myeloid malignancies with trisomy 8 as the sole cytogenetic aberration differ quite extensively with regard to clinical and morphologic features as well as to gene expression patterns [29,127]. This heterogeneity may be explained by different underlying, cytogenetically undetectable genetic changes in AMLs and MDS with +8 as the sole chromosomal aberration. Their identification would be important not only for the understanding of the biology of these disorders, but also for clinical purposes with possible diagnostic and prognostic ramifications.

The cryptic abnormalities may be located at chromosome 8 or involve other chromosomes. To date, and as discussed previously, no evidence for any hidden rearrangements in chromosome 8, at least as ascertained by Southern blot, FISH, and SNP

analyses, has been forthcoming [138,145-147]. However, other methods and investigatory approaches in the future may well identify genetic changes on the chromosome 8 homologues.

A few multicolor FISH studies, comprising a total of 20 AMLs and MDS with isolated +8, have been performed in order to find cryptic chromosome aberrations [147,156-158]. Only one of these cases – an AML in which the G-banding morphology was suboptimal – was shown to harbor an additional anomaly, a t(7;14)(q3?1;q2?2) which was not further characterized [156]. Using subtelomeric multicolor FISH, Brown et al. [159] studied one AML with +8; no cryptic abnormality was detected. In fact, various FISH techniques have, as yet, not provided any evidence for hidden rearrangements in +8-positive AMLs and MDS, with the exception of one AML in which a cryptic insertion of *MLL* into chromosome 9 was reported [160]. Furthermore, Langabeer et al. [161], recognizing that +8 is a common secondary change in t(15;17)(q22;q21)-positive AMLs (Table 7), analyzed 54 AMLs with trisomy 8 for the presence of cryptic *PML*/*RARA* fusions with RT-PCR; no fusion transcripts were found.

Studies of the presence of somatic point mutations of leukemia-associated genes have proved somewhat more fruitful. Thus, several AMLs and MDS with +8 as the sole cytogenetic aberration have been reported to harbor, e.g., *CEBPA, FLT3, KRAS, NRAS*, and *RUNX1* mutations [162-166]. However, none of these mutated genes have proved to be specifically associated with AMLs and MDS with +8.

Very recently, we used high-resolution genome-wide array-based comparative genomic hybridization to look for cryptic abnormalities in 10 AMLs and MDS with trisomy 8 as the sole cytogenetic aberration [167]. Interestingly, this assay revealed karyotypically previously undetected intra-chromosomal imbalances, not corresponding to known genomic copy number polymorphisms, in four of the ten cases. These changes, all of which confirmed by

FISH, comprised both segmental duplications and hemizygous deletions, involving several different chromosomes, although not chromosome 8. Most notably, at least two of the identified changes were certainly leukemia-associated: a del(7)(p14p14), shown to have occurred before the trisomy 8, and a hemizygous deletion of the region surrounding the *ETV6* gene in 12p13. These results, for the first time, show that cryptic abnormalities are frequent in AML/MDS cases with +8 as the seemingly sole change, and also support that trisomy 8 is not sufficient for leukemogenesis.

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Table 1

Frequencies (%) of trisomy 8 in AML.

	M0	M1	M2	M3	M4	M5	M5a	M5b	M6	M7	Spec	NOS	Total
Sole change	5.8	6.0	5.7	1.9	6.4	10	12	12	6.6	4.7	0	8.1	6.3
Overall	12	14	13	9.6	14	22	30	24	22	16	11	20	16

Spec, special type; NOS, not otherwise specified.

The frequencies are based on cytogenetically abnormal AMLs reported in the literature [9]. Only unselected cases were ascertained, i.e., AMLs reported solely because of the presence of trisomy 8 were excluded. The frequencies of +8 as a sole change as well as together with other aberrations vary significantly among the morphologic subtypes ($P<0.001$; chi-square test).

Table 2

Frequencies (%) of trisomy 8 in MDS.

	RA	RARS	RAEB	CMML	RAEBt	Spec	NOS	Total
Sole change	11	13	12	15	9.1	0	6.6	11
Overall	18	24	17	20	19	20	12	17

RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess of blasts; CMML, chronic myelomonocytic leukemia; RAEBt, RAEB in transformation; Spec, special type; NOS, not otherwise specified.

The frequencies are based on cytogenetically abnormal MDS reported in the literature [9]. Only unselected cases were ascertained, i.e., MDS reported solely because of the presence of trisomy 8 were excluded. The frequencies of +8 as a sole change as well as together with other aberrations do not vary significantly among the morphologic subtypes ($P>0.20$; chi-square test).

Table 3

Frequencies (%) of trisomy 8 as the sole change in AML and MDS in relation to age.

	Age (years)									
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100
AML	3.9	6.3	4.2	5.6	7.9	7.7	9.4	8.8	11	50[a]
MDS	7.0	6.6	24	4.9	10	8.3	11	9.0	14	0

[a]This group included only 2 patients, one of whom had +8 as the sole change.

The frequencies are based on cytogenetically abnormal AMLs and MDS reported in the literature [9]. Only unselected cases were ascertained, i.e., AMLs and MDS reported solely because of the presence of trisomy 8 were excluded. The increasing frequency of +8 by age in AML is significant ($P<0.001$); no such trend is seen for MDS ($P>0.30$; Cochran-Armitage trend test).

Table 4

Frequencies (%) of trisomy 8 as the sole change in AML and MDS in relation to geographic origin.

	Africa	Asia	Europe	Latin America	North America	Oceania
AML	5.1	4.3	7.5	5.6	5.0	16.5
MDS	0[a]	9.9	12	6.8	9.3	-[a]

[a]Only one MDS (without +8) from Africa and none from Oceania have been reported.

The frequencies are based on cytogenetically abnormal AMLs and MDS reported in the literature [9]. Only unselected cases were ascertained, i.e., AMLs and MDS reported solely because of the presence of trisomy 8 were excluded. The frequency distribution of +8 as a sole change in AML, but not in MDS, varies significantly among the different continents ($P<0.001$; chi-square test).

Table 5

Clinical characteristics of AML with trisomy 8 as the sole abnormality.

Reference	No. of cases	Median age (range)	Median WBC (range)	CR (%)	Median survival (months)
Berger et al [70]	10	NR	NR	70	16
Yunis et al [65]	15	64 (NR)	NR	NR	10
Dastugue et al [71]	11	NR	NR	91	11
Schoch et al [60]	20	57 (24-76)	9.7 (0.7-127)	70	21
Byrd et al [61]	42	64 (16-79)	7.3 (NR)	59	13.1
Grimwade et al [72]	48	NR	NR	83	NR
Raimondi et al [73]	10	15 (NR)	54 (NR)	80	NR
Grimwade et al [74]	41	NR	NR	51	NR
Byrd et al [75]	41	NR	NR	61	12
Elliott et al. [12]	13	59 (24-72)	9.0 (0.8-66)	85	12
Farag et al. [62]	63	65 (16-80)	5.4 (0.7-241)	56	11
Wolman et al [13]	43	61 (21-78)	6.3 (1.1-80)	67	12.5

WBC, white blood cell count ($x10^9$/l); NR, not reported, CR, complete remission.

Table 6

Clinical characteristics of MDS with trisomy 8 as the sole abnormality.

Reference	No. of cases	Median survival (months)	Evolution to AML (%)
Yunis et al [65]	9	18	NR
Nowell and Besa [77]	7	11	57
Solé et al [78]	8	11	38
Morel et al [79]	12	25	8
Solé et al [11]	31	13	42
Bernasconi et al [14]	16	NR	62

NR, not reported.

Table 7

Frequencies of +8 as a secondary change to primary inversions and translocations in AML[a].

Primary change	+8 (%)	Primary change	+8 (%)
t(1;3)(p36;q21)	0	t(7;12)(q36;p13)	25
t(1;11)(p32;q23)	18	t(8;16)(p11;p13)	5.2
t(1;11)(q21;q23)	0	t(8;21)(q22;q22)	4.8
t(1;22)(p13;q13)	0	t(9;11)(p21;q23)	19
t(2;11)(p21;q23)	4.3	t(9;22)(q34;q11)	16
inv(3)(q21q26)[b]	2.2	t(10;11)(p12;q23)	8.9
t(3;12)(q26;p13)	0	t(11;17)(q23;q21)	9.4
t(3;21)(q26;q22)	11	t(11;17)(q23;q25)	11
t(4;12)(q12;p13)	4.8	t(11;19)(q23;p13)	12
t(6;9)(p22;q34)	6.8	t(15;17)(q22;q21)	12
t(6;11)(q27;q23)	4.9	inv(16)(p13q22)[c]	9.8
t(7;11)(p15;p15)	5.0	t(16;21)(p11;q22)	7.9

[a]Based on Mitelman et al [9].

[b]Includes cases with t(3;3)(q21;q26).

[c]Includes cases with t(16;16)(p13;q22).

Table 8

Frequencies of +8 together with other anomalies in MDS[a].

Other change	+8 (%)	Other change	+8 (%)
idic(X)(q12-13)	0	del(12p)	10
-Y	13	del(13q)	7.1
der(1;7)(q10;p10)	22	-17	17
-5	16	del(17p)	20
del(5q)	12	-18	11
-7	7.8	+19	36
del(7q)	11	del(20q)	7.9
del(11q)	16	+21	28

[a]Based on Mitelman et al [9].