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SHORT COMMUNICATION

Only particular cytogenetic events are related to disease progression in sequential cytogenetic studies in myelodysplastic syndromes

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Summary

We performed prospective sequential cytogenetic studies in 76 patients with myelodysplastic syndromes (MDS) followed up to 82 months. Their karyotypes were followed routinely, regardless of clinical status. The incidence of evolutive karyotypes was similar in patients with a normal karyotype at referral and in patients with clonal abnormalities at diagnosis (24.5 and 26.1%, respectively). We did not find association between karyotype evolution and leukemic transformation or reduced survival, since the majority of secondary cytogenetic changes in evolutive karyotypes of our patients were aberrations with good or intermediate prognosis. Therefore, we concluded that only particular cytogenetic events are related to disease progression, while others represent secondary changes of little biologic and prognostic significance.

Key words: *cytogenetics, follow up, karyotype, myelodysplastic syndromes, prognosis*

The nature, incidence and prognostic significance of clonal karyotype abnormalities in MDS has been extensively investigated in a number of studies. Although the prognostic relevance of cytogenetics is generally appreciated, the prognostic value of cytogenetic evolution has rarely been precisely evaluated [1-7]. Recently, Wang and colleagues [1] retrospectively analyzed the cytogenetic features at diagnosis and during follow-up in 85 patients with primary MDS. They found cytogenetic evolution in 21% of the patients, with chromosomes 8, 5, and 1 most frequently involved. Patients with higher levels of marrow blasts, aggressive WHO subtypes and higher IPSS risk had higher incidence of developing cytogenetic evolution. Median survival and time to progression of patients with cytogenetic evolution were significantly shorter than in patients without cytogenetic evolution. However, prospective sequential cytogenetic studies in MDS during extended follow-up periods were carried out only by the group from the University Hospital of Wales [2-4]. Their patients were followed routinely, regardless of clinical status and with no selection (patients with normal karyotype at referral every 12 months and patients with clonal abnormalities at diagnosis every 6 months). We used the same methodology during our sequential cytogenetic studies of 76 patients in whom more than one karyotype was analyzed (mean 2.25, range 2-4). Patients were followed up to 82 months (median 34). Cytogenetic evolution occurred in 19/76 (25%) patients. The incidence of cytogenetic evolution did not correlate to different WHO subtypes of MDS. The most frequently occurring clonal abnormalities in evolved karyotypes were del(5q) in 3 cases, and monosomy 7, del(20q), del(6q) and trisomy 21 each in 2 cases. Other clonal abnormalities (disclosed in one case each) were del(9q), 11p+, del(21q), del(17q), +14, marker chromosome and multiple abnormalities. In 13 cases, cytogenetic evolution took place in patients with an apparently normal karyotype at referral after a median follow-up time of 26 months (range 4-74).

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In the remaining 6 cases, additional changes were detected in patients with clonal abnormalities at referral after a median follow-up time of 9.5 months (range 5-16). The incidence of cytogenetic evolution was almost identical in patients with a normal karyotype at referral (13/53=24.5%) and in patients with clonal abnormalities at diagnosis (6/23=26.1%). Leukemic transformation occurred in 6 of 13 cases with evolved karyotypes that presented with normal karyotype, and in 4 of 6 cases with clonal karyotype abnormality at referral. Clonal abnormalities which were not associated with leukemic transformation either in patients with normal karyotype or in patients with abnormal karyotype at referral were del(5q), del(9q) and 11p+. Time to leukemic transformation in patients with cytogenetic evolution in normal karyotype at referral was longer than in patients with cytogenetic evolution in abnormal karyotype at referral (49 vs 32 months), but this difference was not statistically significant (log-rank test; p=0.26). Similarly, median overall survival in patients with cytogenetic evolution in normal karyotype at referral was twice as long than in patients with cytogenetic evolution in abnormal karyotype at referral (60 vs 35 months), but this difference was significant only at the p=0.06 level.

Since most studies suggest an association between karyotype evolution, disease progression and reduced survival [1-7], we critically analyzed differences between our results and previously published data. We noticed than the majority of secondary cytogenetic changes in evolutive karyotypes of our patients were aberrations with good or intermediate prognosis [8]. Therefore, we concluded that only particular cytogenetic events are related to disease progression, while others represent secondary changes of little biologic and prognostic significance. We also emphasized the need to distinguish between the two different pathobiological processes: "clonal evolution" and "clonal expansion". Only "clonal evolution" is associated with clinical disease progression, whilst "clonal expansion" may represent an expansion of already existing, but hitherto unrecognized clone (technically speaking, undetected in 20 metaphases routinely done at refferal), or intraclonal evolution with the emergence of new cytogenetic subclones without additional malignant potential.

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