

inv(3)(q21q26) in AML/MDS: monitoring the malignant clone with interphase FISH

inv(3)(q21q26) and t(3;3)(q21;q26) are characteristic abnormalities of acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and myeloproliferative diseases (MPD).¹⁻³ These aberrations are often associated with dysmegakaryopoiesis and, clinically, a poor treatment outcome even with the most potent anti-leukemic treatment modalities.¹⁻⁴ The EVI-1 oncogene may be overexpressed in these cases.⁵ Although 3q rearrangements are thought to be specific aberrations in AML with multilineage dysplasia, an entity recently described in the WHO classification of hematologic neoplasms,^{6,7} the distribution of these abnormalities among true de novo AML, MDS and MDS-related AML remains unclear. In contrast to other types of chromosome rearrangements, polymerase chain-reaction (PCR) based assays for the detection and monitoring of 3q aberrations are not available for clinical routine investigations.⁸ We recently established an interphase FISH assay for the detection of 3q21 rearrangements⁸ and report on the monitoring of the malignant clone in a patient with inv(3)(q21q26).

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Case report. A 57-year old Caucasian male was diagnosed with de novo AML. Bone marrow (BM) biopsy showed infiltration with 70% blast cells (CD 13+, 15+, 33+, 43+); there was no evidence of myelodysplasia/dysmegakaryopoiesis. Cytogenetic examination of the BM revealed the karyotype: 46,XY, inv(3)(q21q26). The patient received four courses of myeloablative chemotherapy and was considered in complete remission. Relapse was diagnosed after 2 months; the patient achieved a partial remission after reinduction chemotherapy. A matched sibling donor allogeneic stem cell transplantation (allo-SCT) was performed (conditioning regimen: fractionated total body irradiation and high-dose cyclophosphamide); BM examination on day +28 showed trilineage engraftment with no residual AML; however, the patient relapsed on day + 89 and died of septicemia on day + 110. The interphase FISH assay for detection of inv(3)(q21q26) became available for this patient after the 5th course of chemotherapy. After regeneration of the peripheral blood (PB) counts, bone marrow biopsy showed 7% residual blast cells; the PB differential count showed bands 3%, segmented 42%, lymphocytes 25% and monocytes 30%. However, interphase FISH analysis at this time revealed 70% aberrant signals in PB. After allo-SCT, there were no pathologic FISH signals in PB (day +15, +28 and +56) and BM (day +28), consistent with successful engraftment. These findings were confirmed by BM immunohistochemistry as well as fluorescence activated cell sorting (FACS) analysis of PB and BM. On day +89 FISH revealed 30% pathologic signals in BM; clinical relapse was confirmed by BM FACS analysis, BM histology and immunohistochemistry (30% blast cell infiltration). On day +103 the

PB differential count was normal, but FISH showed 27% pathologic signals in PB. Based on morphological criteria only, the distinction between de novo AML and MDS-related AML may be difficult. The high percentage of pathologic FISH signals in the regenerating PB after the 5th course of chemotherapy and the absence of blast cells at this time clearly demonstrate that the malignant clone in this case also comprised well differentiated PB cells. On day +103 after allo-SCT, cells exhibiting signal patterns indicative of the 3q rearrangement again outnumbered cells with blast cell morphology. These data strongly suggest an underlying myelodysplastic syndrome in this patient whose initial diagnosis was de novo AML. Thus, the patient was presumably overtreated, receiving five courses of myeloablative chemotherapy, and might have benefited from allo-SCT performed earlier in the course of the disease. In summary, interphase FISH may allow a better distinction of de novo AML and MDS associated with 3q rearrangements. Apart from being a matter of basic pathologic evaluation, important treatment decisions may be based on both an exact initial diagnosis as well as assessment of residual disease after therapy. Especially in cases of MDS-like disease, interphase FISH facilitates sensitive monitoring of MRD after allo-SCT. Relapse after allo-SCT is most imminent in patients with these genetic aberrations;⁴ early identification of recurrence of the malignant clone is highly desirable in order to initiate immunomodulatory therapies quickly, e.g. cessation of immunosuppression or donor lymphocyte infusions. Thus, interphase FISH may be a valuable tool to improve treatment outcome of patients with 3q rearrangements.

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References

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