S-HM-3

Sustained and Repeated Response of Relapsed Acute Promyelocytic Leukemia (APL) to Arsenic Therapy

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Background: We have previously reported on the early experience of the use of arsenic (As2O3) infusion in the treatment of 8 cases of relapsed acute promyelocytic leukemia (APL). The follow up (FU) result of a larger cohort of 14 cases is updated and the pattern of relapse and response to further therapy is presented.

Material and Methods: 14 consecutive cases of relapsed APL (13 R1, 1 R2) were treated with intravenous Ar2O3 (10mg/day) till remission (CR). This was consolidated with three courses of idarubicin (total dose 56mg/m2). The presence of minimal residual disease (MRD) in the marrow was measured with PML-RARA RT-PCR. The expression level of mRNA for the multidrug resistance (MDR) protein was quantified in the marrow, in arbitrary units, by Taqman Q-PCR. Post-arsenic relapses were retreated with a combination of Ar2O3 (10mg daily) and ATRA (45mg/m2 daily) till CR.

Results: The median age was 33 (range 12 to 48), with a male to female ratio of 8:6. The median time to relapse was 14 months (range 7 to 24). A CR was achieved in all cases, including two patients with extramedullary disease (EMD) in the ear. The median time to response was 38 days. There was no MRD detectable after consolidation and in all patients currently in remission. The median FU was 22 months (range 2 to 28), and three patients relapsed at 10,12 and 18 months after Ar2O3 respectively. One patient relapsed in the brain and died. Two cases were retreated with As2O3 for 62 and 73 days in combination with ATRA and achieved hematological remission again. However MRD was still detectable in the two cases at 2 and 5 months after second As2O3. The overall side effects included transient hepatitis (n=2), vascular leak syndrome (n=2) and peripheral neuropathy (n=1). The median MDR mRNA levels in APL marrow before and after exposure to Ar2O3 and idarubicin relapse were 420 units (6 to 4995) and 1685 units (717 to 13138) respectively. The median level at diagnosis was 93 units (28 to 580).

Conclusions: As2O3 is a uniformly safe and effective treatment for APL relapse. Durable MRD eradication can be achieved. It is useful for EMD as well marrow disease. High MDR levels at advanced relapse did not affect Ar2O3 efficacy. As2O3 is also effective for re-treatment although longer duration of treatment and synergism with ATRA may be needed.

S-HM-4

Methylation of p15 and p16 genes in Acute Promyelocytic Leukemia: Potential Diagnostic and Prognostic Significance

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Background: To investigate the frequency of p15 and p16 gene promotor methylation in acute promyelocytic leukemia (APL), as well as to define its value in the detection of minimal residual disease (MRD) and treatment prognostication.

Patients and Methods: Bone marrow DNA from 26 APL patients at diagnosis and during follow-up were studied with the methylation-specific polymerase chain reaction (MSP). Serial marrow DNA was studied by MSP for MRD and survivals (DFS and OS) were correlated with p15 methylation status at diagnosis.

Results: MSP for p16 and p15 gene methylation has a maximum sensitivity of 10^{-4} and 10^{-5}. At diagnosis, nineteen patients (73.1%) showed p15 methylation, whereas only three patients (11.5%) showed p16 methylation, all of whom had concomitant p15 methylation. During follow-up, p16 methylation was acquired in two patients, one during the third hematologic relapse, and the other during transformation into a therapy related myelodysplastic syndrome. Six patients were evaluated serially with MSP for p15 methylation at diagnosis and during follow up. In two patients, persistent p15 methylation despite morphologic remission preceded subsequent hematologic relapses. In two cases, p15 methylation persisted after chemotherapy induced remission, but disappeared after allogeneic bone marrow transplantation, which led to prolonged remission. In two other cases, p15 methylation was transiently detected after remission but disappeared with further chemotherapy, resulting in durable remission. The five-year disease-free survival of patients with p15 methylation was significantly inferior to those without p15 methylation (15% versus 62.5%, $p = 0.02$) and this remained significant in multivariate analysis.

Conclusion: p15 but not p16 gene methylation is frequent in APL. p16 methylation might be acquired during clonal evolution. p15 methylation is a potential marker of MRD in APL, and might be of prognostic significance.