C-H-4

Quantification of the *Multidrug Resistance - 1* Gene Expression in Relapsed Acute Promyelocytic Leukaemia Treated with Arsenic Trioxide

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Introduction: The P-glycoprotein, encoded by the *multidrug resistance-1* (*MDR-1*) gene, is a transmembrane efflux pump for chemotherapeutic agents. Expression of *MDR-1* may confer multidrug resistance to cancer cells. Arsenic trioxide (As_2O_3) is an effective treatment for acute promyelocytic leukaemia (APL) in relapse. However, chemotherapy is needed to consolidate As_2O_3-induced remissions. The expression of *MDR-1* may therefore affect the efficacy of As_2O_3/chemotherapy.

Materials and Methods: *MDR-1* gene expression in 16 patients with relapsed acute promyelocytic leukaemia (APL) treated with As_2O_3 and consolidated with idarubicin was quantified by quantitative polymerase chain reaction. The results were normalized with an internal control gene (*GAPDH*), and compared against a standard from the *MDR-1* expressing cell line CEM1.0.

Results: *MDR-1* expression was low (median 18×10^{-3} (4-282) CEM1.0) at presentation. However, *MDR-1* expression was increased in nine patients (56%) at relapse (median 4,082 (75-223,376) $\times$ 10^{-3} CEM1.0). The response of the APL to As_2O_3 was independent of the *MDR-1* gene expression, as all patients achieved a remission. Six patients relapsed again after As_2O_3-induced remissions that were consolidated with idarubicin. *MDR-1* expression prior to treatment with As_2O_3 / chemotherapy did not correlate with subsequent relapses. The *MDR-1* was further up-regulated in about half of the patients with subsequent relapses.

Conclusions: We conclude that *MDR-1* expression is low in APL at presentation, but up-regulated in about half of the patients at relapse. *MDR-1* expression does not influence the response to As_2O_3, or subsequent relapses. Therefore, the increased *MDR-1* expression in relapsed APL may be overcome by As_2O_3. Factors other than *MDR-1* expression may be involved in relapses post-As_2O_3 treatment.

C-H-5

Sustained and Repeated Response of Relapsed Acute Promyelocytic Leukaemia to Intravenous or Oral Arsenic Trioxide

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Introduction: Over 90% of patients with acute promyelocytic leukaemia (APL) will achieve complete remission (CR) with all trans retinoic acid (ATRA) and anthracycline containing regimens. However, 30% of cases still relapse. Drug therapy remains the mainstay of treatment for relapsed APL, as results of allogeneic bone marrow transplantation are poor.

Material and Methods: From August 1998 to November 2001, 22 cases of APL in relapse were treated with intravenous (iv) or oral arsenic trioxide (As_2O_3, 10mg/day). The median age was 39 (8–72) years. The relapse was medullary in twenty cases, and extramedullary (external auditory canal) in two cases. Concomitant medical diseases included tetraplegia (n=1), mantle cell lymphoma (n=1) and end stage renal failure on peritoneal dialysis (n=1).

Results: A CR was achieved in all cases (100%), at a median of 38 days of As_2O_3 treatment. After idarubucin consolidation (total dose: 54 mg/m^2) and at a median follow-up of 13 months, 9 patients (41%) had relapsed again. Two patients died of cerebral bleeding before further treatment could be given. Seven patients (78%) achieved further CR with combined As_2O_3+ATRA (45mg/m^2/day). This was further consolidated with six courses of As_2O_3+ATRA (for 14 days every 4-6 weeks). Since July 2001, all courses of As_2O_3 were given as oral out-patient therapy (total: 25 courses). There was no significant difference in the pharmacology or clinical efficacy between in-patient iv and out-patient oral As_2O_3 therapy. No significant neutropenia or sepsis occurred in any patient on As_2O_3 or As_2O_3+ATRA in any form. Side effects included transient hepatitis (n=2), vascular leak syndrome (n=2), peripheral neuropathy (n=1) and headache (when As_2O_3 was combined with ATRA, n=3). There was no prolonged QT interval or arhythmia. Minimal residual leukaemia, as reflected by *PML/RARA* detectable with nested reverse transcription polymerase chain reaction, was not found in 19 patients in CR.

Conclusion: Oral or iv As_2O_3 ± ATRA is a highly efficacious treatment for relapsed APL. The response to As_2O_3 is preserved even in advanced relapses.