The Development of Arsenic as an Anti-cancer Drug

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Background:

Arsenic has been used in the treatment of diseases for centuries, both in Western and Chinese medicine. Arsenic exists in three natural forms as arsenic trioxide, diarsenic trisulphide, and tetra-arsenic tetrasulphide. The use of arsenic was popularized in the eighteenth century when a solution of arsenic trioxide was formulated (Fowler's solution). The effect of arsenic trioxide in leukemia treatment was first recorded at the end of the nineteenth century. In Hong Kong, arsenic trioxide used to be the standard treatment for leukemia until early 1950s. It fell out of use with the advent of newer chemotherapeutic agents. The efficacy of arsenic trioxide in acute promyelocytic leukemia (APL) was discovered initially in Harbin, China, and was confirmed by a research group in Shanghai. To date and outside Hong Kong, arsenic is only available in the intravenous formulation.

Materials and Methods:

As arsenic used to be given orally, we investigated the possibility of re-formulating arsenic trioxide. An oral formulation of arsenic trioxide was subsequently successfully formulated.

Results:

Pharmacokinetic studies showed that oral arsenic trioxide achieved a bio-availability comparable to that of the intravenous formulation. Since 2000, all arsenic trioxide therapy has been given as the oral formulation. We showed that in relapsed APL, arsenic based therapy was superior to chemotherapy or bone marrow transplantation. Furthermore, in a study involving 40 patients with relapsed APL treated by a regimen based on arsenic without bone marrow transplantation, 39 patients (97.5%) achieved complete remission (CR) after initial arsenic trioxide treatment. Twenty-two patients received oral arsenic trioxide maintenance, which significantly decreased further relapses (2/22 with *versus* 10/17 without arsenic trioxide maintenance, p=0.001; median follow-up: 26 months). Nine of ten post-arsenic trioxide relapses achieved CR with arsenic trioxide and all trans retinoic acid, eight of whom had remained in remission (median follow-up: 33 months). One patient relapsing post-arsenic trioxide / all trans retinoic acid responded to arsenic trioxide / all trans retinoic acid / ascorbic acid, and had remained in CR5. All patients in continuous remission were *PML/RARA* negative by polymerase-chain-reaction (PCR). Quantitative-PCR showed progressive up-regulation of the *multidrug resistance-1* gene with relapses, suggesting that the otherwise use of chemotherapy might be ineffective. Ongoing clinical trials are also testing the efficacy of arsenic trioxide in multiple myeloma. Laboratory data show that arsenic trioxide is effective in a much wider range of neoplastic disorders, suggesting that it may be of therapeutic benefit.

Conclusion:

Arsenic trioxide is effective in APL, and has promise in other neoplastic disorders. Oral formulation of arsenic trioxide is efficacious, and makes long term treatment with arsenic a reality.