develop circulating antibodies against Sp17 as evidence supporting the in vivo safety of targeting Sp17 for immunotherapy is dubious at best.

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References

1. Lacy HM, Sanderson RD. Sperm protein 17 is expressed on normal and malignant lymphocytes and promotes heparan sulfate-mediated cell-cell adhesion. Blood. 2001;98:2160-2165.
2. Lim SH, Wang Z, Chiriva-Internati M, Xue Y. Sperm protein 17 is a novel cancer-testis antigen in multiple myeloma. Blood. 2001;97:1508-1510.
3. Wen Y, Richardson RT, Widgren EE, O'Rand MG. Characterization of Sp17: a ubiquitous three-domain protein that binds heparin. Biochem J. 2001;357:25-31.

To the editor:

Severe neurotoxicity following arsenic therapy for acute promyelocytic leukemia: potentiation by thiamine deficiency

Approximately 40% of subjects with acute promyelocytic leukemia (APL) who are given arsenic develop neuropathy symptoms,[1] which are generally mild and will resolve after completion of arsenic treatment. However, severe Guillain-Barre–like neuropathy occasionally occurs and can be crippling.[2] We recently witnessed severe neurotoxicity during arsenic therapy in a subject with occult thiamine deficiency. In analogy to electrolyte disturbance potentiating the occurrence of arrhythmia during arsenic therapy,[3] this might suggest potentiation of thiamine deficiency and arsenic in the genesis of neurotoxicity. The enzyme complex pyruvate dehydrogenase (PDH) in the glycolysis pathway can be one site where thiamine and arsenic interact.[4] PDH requires thiamine as a cofactor for pyruvate decarboxylation, which is also the enzyme very sensitive to inhibition by arsenic at micromolar concentrations,[5] a level achievable with arsenic therapy.[6] Three weeks of oral arsenic in the rat can reduce liver PDH activity by a half.[7] Thus, arsenic therapy can inhibit further the readily diminished PDH activity from thiamine deficiency and adversely affect tissue heavily dependent on carbohydrates for energy provision, such as neural tissue. During the era when arsenic was used as arsphenamine for the treatment of syphilis, a Canadian group had reported the temporal relationship of blood pyruvate elevation and encephalopathy during arsenic treatment in subjects with thiamine deficiency.[8] Those with thiamine deficiency had higher blood pyruvate elevation during therapy and were more prone to developing encephalopathy.

A vegetarian woman, aged 46, with relapsed APL, t(15:17), was given arsenic trioxide 10 mg/d for 28 days. Her first induction with all-*trans* retinoic acid and daunorubicin a year ago was uncomplicated. Medical history was unremarkable. In particular, there was no prior neurological disorder. Her diet was mainly refined rice and leafy vegetables, very sparse in meat and beans. Starting from day 17, she experienced nausea and vomiting. Pain and congestion were noted over the tongue, throat, and conjunctiva. On day 33, she complained of numbness over lower limbs. Confabulation was absent. On day 37, all 4 limbs were paralyzed and areflexic. Speech was inaudible and bulbar paralysis was noted. She sweated heavily and had a vesicular rash over her body. Cerebrospinal fluid showed white count, 1/μL; protein, 0.5 gm/L; and glucose, 6.7 mM. Studies for Venereal Disease Research Laboratory, bacteria, fungus, virus, and oligoclonal band were negative. Nerve conduction study detected generalized reduction of sensory action potential. Motor conduction was normal, while electromyogram showed active denervation. Drug review did not suggest a neurotoxic side effect from any supportive medication. With cranial magnetic resonance imaging (MRI), lesions consistent with Wernicke syndrome were seen over tectum, periaqueductal gray, and periventricular white matter of the third ventricle, both thalami, and the dorsal medulla (Figure 1A,B). The low level of red cell (RBC) transketolase (24 μmol/min L; normal 45-90 μmol/min L), which increased by 32% after in vitro

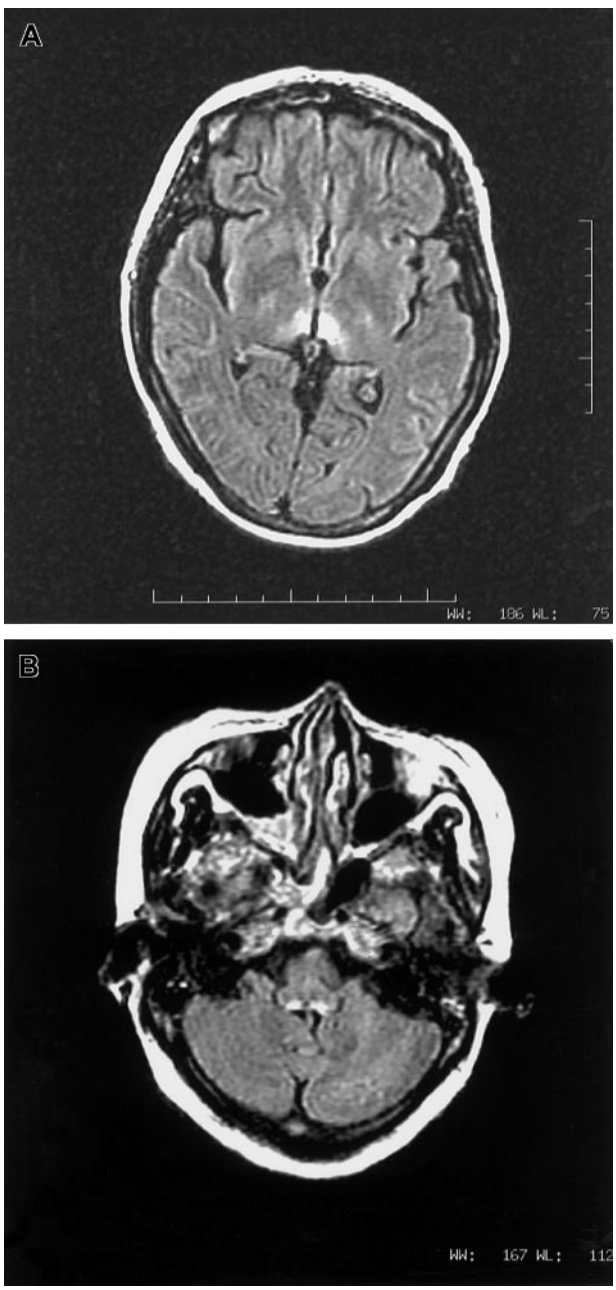

Figure 1. (A,B) MRI images in axial fluid attenuated inversion recovery sequence showing T2-weighted hyperintense lesions surrounding third ventricle (1A) and dorsal aspect of medulla (1B).

addition of thiamine pyrophosphate, confirmed thiamine deficiency. Parental thiamine 100 mg/d was given. The next day, power of the upper limbs dramatically improved and speech became audible. Over the next 5 days, upper limbs regained full power. As_2O_3 at 5 mg/d for 28 days as maintenance was given 5 weeks later, with oral thiamine. There was no deterioration in neurology. Lower limb power continuously improved. RBC transketolase during arsenic maintenance was normal, and MRI scan demonstrated complete resolution of all previous abnormalities.

Rapidly progressive neuropathy with a dose level of 10 mg/d and cumulative dose of 280 mg As_2O_3 is unusual. Moreover, recovery of APL subjects from severe neuropathy had been slow in previous arsenic trials.[1,2] The rapid improvement in our subject after thiamine administration would not signify a pure arsenic toxicity but would support a contributory role of thiamine deficiency in development of an early severe neurotoxicity during arsenic administration. We have no idea yet whether thiamine or its deficiency has any role in the more frequent but milder form of sensory neuropathy. Yet, we recommend an adequate intake of thiamine during arsenic therapy, and we suggest thiamine deficiency be considered when severe neurotoxicity during arsenic is encountered.

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References

1. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol. 2001;19: 3852-3860.
2. Densmore JJ, Hess CE, Ross M. Sensorimotor polyneuropathy following arsenic trioxide therapy for relapsed acute promyelocytic leukemia [abstract]. Blood. 1999;94(suppl 1):228b.
3. Singer JW. Cardiac toxicity of arsenic trioxide [letter]. Blood. 2001;98:1633.
4. Peters RA. Biochemistry of some toxic agents; I, present state of knowledge of biochemical lesions induced by trivalent arsenical poisoning. Bull John Hopkins Hosp. 1955;97:1-20.
5. Hu Y, Su L, Snow ET. Arsenic toxicity is enzyme specific and its effects on ligation are not caused by the inhibition of DNA repair enzymes. Mutat Res. 1998; 408:203-218.
6. Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL); II, clinical efficacy and pharmacokinetics in relapsed patients. Blood. 1997;89:3354-3360.
7. Schiller CM, Fowler BA, Woods JS. Effects of arsenic on pyruvate dehydrogenase activation. Environ Health Perspect. 1977;19:205-207.
8. Sexton GB, Gowdey CW. Relationship between thiamine and arsenic toxicity. Archives of Dermatology and Syphilology. 1969;56:634-647.

To the editor:

Successful double bone marrow and renal transplantation in a patient with Fanconi anemia

In Fanconi anemia (FA), bone marrow failure (BMF) is the major cause of morbidity and mortality, whereas renal failure is less frequent with a possibly underestimated occurrence of between 25% and 30%[1,2] and has a lower impact on survival. Bone marrow transplantation (BMT) provides a survival rate of greater than 80% from sibling donors[2] and of about 30% from unrelated donors.[3,4]

We present a peculiar case of a patient with FA who, due to clinically prevalent BMF, underwent BMT that was followed by renal transplantation (RT) for end-stage renal disease.

This male patient presented at birth with renal failure caused by congenital single hypoplastic kidney. At the age of 3.5 years, because of thrombocytopenia (74×10^9/L) and a positive dyepoxibutane test, he was diagnosed with FA. At the age of 4.5 years serum creatinine was 278 μM, white blood cells (WBCs) were 3.7×10^9/L, neutrophils 1×10^9/L, Hb 9 g/dL, and platelets 36×10^9/L. At this stage the patient, without previous transfusions, underwent BMT (Table 1).

Two years after the graft, a further impairment of renal function required peritoneal dialysis, and 3.5 years after BMT, the patient underwent RT from a 9-year-old, B-positive, cytomegalovirus (CMV)–positive/Epstein Barr virus (EBV)–negative cadaveric donor. Donor and recipient shared one HLA allele at locus A and one at locus DRB1. Serum creatinine normalized (53 μM) 5 days after the transplant. cyclosporin A (CyA) and steroids were given as posttransplant immunosuppression. No acute rejection occurred during the follow-up.

Table 1. BMT characteristics

	Characteristic
Donor	HLA identical brother
ABO match	Donor B pos, Rec 0 pos
Conditioning regimen	Cy 20 mg/kg recipient body weight + TAI 500 cGy
Cell infused	19.8×10^8/kg
GVHD prophylaxis	CyA 3 mg/kg. Then reduced to maintain serum through levels between 50-100 ng/mL for 15 months
Engraftment	PMN ($> 0.5 \times 10^9$/L) day + 8, Plt ($> 50 \times 10^9$/L for 3 consecutive days) day + 35
Toxicity	Grade I mucositis
GVHD	No

Currently, 6 years from BMT and 2.2 years from RT, still on steroids and CyA, the patient is well, with no evidence of tumors. WBCs are 7.4×10^9/L; PMN, 4.7×10^9/L; Hb, 10.1 g/dL; and platelets, 188×10^9/L. The hemopoiesis (short tandem repeat polymorphism analysis on peripheral blood) is entirely of donor origin. Serum creatinine is 78 μM.

To the best of our knowledge, this is the first FA patient who underwent a double sequential BMT and RT.

Although double BMT and RT have already been performed,[5-8] in the context of FA, this experience is peculiar. In fact, in FA patients who have a cancer "proneness" per se, BMT constitutes an additional risk factor for tumors because of the irradiation and alkylating agents used in the conditioning regimen, chronic graft-versus-host disease (cGVHD) occurrence, and posttransplantation immunosuppression.[2,9,10] RT represents another risk factor because of the immunosuppression.

Our patient has a high risk of late cancers. In fact, apart from GVHD, he has all the other risk factors, mainly those related to the high immunosuppression load that was required by the 2 sequential transplants from 2 different donors. The choice of an EBV-negative renal donor aimed to diminish the cancer risks by reducing the chances of primary EBV infection which, in turn, is the major risk factor for posttransplant lymphoproliferative disorders.[11]

No tumors have occurred thus far in our patient during his 6-year follow-up. However, since in FA patients malignancies appear at a mean of 8.2 years after BMT,[10] a careful lifetime cancer monitoring looks mandatory.

This case outlines the relevance of renal malformations on the outcome of the FA patients. In addition, it shows that sequential BMT