Aplastic anemia (AA) is a bone marrow hemopoietic dysfunction syndrome caused by various factors. Its hematological characteristic is peripheral pancytopenia. Wide and thorough researches have been carried out in the past 10 years, and long-term disease free survival of the patients has become significantly elevated. However, the mortality of very severe aplastic anemia (VSAA) patients remains about 50%, with obviously low bone marrow proliferation, complications of serious infection, and visceral hemorrhage frequently present in patients, and most of them die within one year.

Considering that VSAA is characterized by an abrupt onset, rapid development, progressive anemia, high fever, severe hemorrhage, etc., the disease is categorized as "Jilao (急劳)", "Relao (热劳)", and "Xuezheng (血证)" in Chinese medicine (CM). In 2004, it was nominated by the Special Committee of Hematology, Chinese Association of Integrative Medicine as "Jisuilao (急髓劳)". Our department has engaged in integrative medical research and the clinical treatment of AA for over 50 years, and

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ABSTRACT  Objective: To explore the prognostic factors for very severe aplastic anemia (VSAA) patients treated mainly with Chinese Kidney (Shen)-invigorating drugs (CKID) combined with anti-lymphocyte globulin (ALG) or anti-thymocyte globulin (ATG). Methods: Twenty-seven VSAA patients were treated with CSKD+ALG/ATG therapy in conjunction with cyclosporine A, androgen, hemopoietic growth factor, etc. The relationship of the effectiveness and some factors (age of patients, course of illness, blood and bone marrow figures, etc.) were analyzed. Results: In the 25 evaluated VSAA patients who had been followed up for over 1 year, 9 patients (36.0%) were basically cured, 5 (20.0%) remitted, 6 (24.0%) were markedly improved, and 5 (20.0%) were treated in vain, with the total effective rate of treatment being 80.0% (20/25). Better clinical therapeutic effects were shown in patients newly diagnosed with VSAA, of male sex (P=0.037), >20 years old (P=0.045), with an illness course <1 month (P=0.048), with peripheral neutrophil count >0.1 × 10^9/L (P=0.023), and with reticulocyte count >10 × 10^9/L (P=0.002). Platelet count (P=0.820) and bone marrow lymphocyte percentage (P=0.736) showed no correlation with the therapeutic effectiveness. Multi-factor analysis by the Kaplan-Meier procedure on the factors influencing survival showed that rather longer survival times occurred in patients >20 years old, with peripheral neutrophil count >0.1 × 10^9/L, reticulocyte count <10 × 10^9/L, and platelet count >10 × 10^9/L (all P=0.0001). Bone marrow lymphocyte percentage and the initiation time of ALG/ATG application (from onset of the illness) showed no significant influence on patients' survival time (P=0.085 and P=0.935, respectively). Conclusions: CSKD+ALG/ATG therapy for treatment of VSAA could enhance the current clinical therapeutic effects and elevate patients' survival rate. Conditions including male sex, age >20 years, illness course <1 month, neutrophil count >0.1 × 10^9/L, and reticulocyte count >10 × 10^9/L are the likely effective indices for predicting favorable therapeutic effectiveness in newly diagnosed VSAA patients.

KEYWORDS  acute aplastic anemia, very severe aplastic anemia, Chinese Kidney-invigorating drugs, anti-lymphocyte globulin, anti-thymocyte globulin
propose to treat chronic AA by centering on Kidney (Shen)-invigoration, which has become the common accepted optimal treatment modality nowadays. Beginning in the 1990s, we started using the Chinese Kidney-invigorating drug (CSKD) combined with anti-lymphocyte globulin (ALG) or anti-thymocyte globulin (ATG) for treating VSAA. Good effectiveness has been achieved, and it has rarely been reported before. In this paper the outcomes of treating VSAA during the period from 1992 to 2009 using integrative medicine are reported.

METHODS

Diagnostic Standard

Based on the standard of severe aplastic anemin (SAA) submitted by Camitta (1976), patients with an additional condition of neutrophil count <0.2 × 10^9/L were diagnosed as VSAA.

General Materials

All subjects enrolled were in-patients of the Department of Hematology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, from 1992 to 2009, and were newly diagnosed with VSAA. A total of 27 patients were included, with 19 males and 8 females, ages between 7–64 years with a median age of 30.1 years, and a course of illness between 1–6 months, with a median of 1.1 months.

Treatment

Pig ALG was applied to 16 patients, and ATG (horse ATG for 5 and rabbit ATG for 6) was applied to 11. The pig ALG was a product of Wuhan Institute of Biologicals, China, at a dosage of 20–30 mg/(kg•d). ATG was selected from one of the following: (1) horse ATG [product of Genzyme Polyclonals S.A.S, France, 8.3–13.4 mg/(kg•d)]; (2) rabbit ATG [product of Genzyme Polyclonals S.A.S, French, 2.5–3.2 mg/(kg•d)]; and (3) rabbit ATG [product of Fresenius Biotech GmbH, Germany, 5–7 mg/(kg•d)]. After the patients passed sensitivity tests, the remedy was administered by intravenous drip slowly once a day for 5 successive days, complemented with dexamethasone 5 mg (placed in a pot) and promethazine hydrochloride 25 mg (muscular injection) at each time of administration.

Supportive care: all patients selectively received the auxiliary treatment as follows: (1) cyclosporin A (CsA), initiated at 3 mg/kg twice a day orally; the dosage was adjusted depending on the drug concentration in blood to maintain a valley concentration within 200–400 ng/mL for over half a year until steady blood level values presented, then the dose was diminished gradually and withdrawn completely at the termination; (2) androgen (stanozolol 6–12 mg/d or testosterone undecanoate capsules 120–240 mg/d) was being administered orally 3 times to keep normal range in peripheral blood, and the dosage was then allowed to diminish and be maintained for about 3 years; (3) granulocyte colony stimulating factor 5 μg/kg was given daily until neutrophil counts were >1 × 10^9/L; (4) blood infusion: an infusion of concentrated erythrocyte was given when hemoglobin was <60 g/L, and platelet transfusion was implemented when platelet count was <10 × 10^9/L or there was an appearance of severe hemorrhagic tendency.

CSKD treatment was carried out based on the Shen-invigorating theory of CM. Syndromes in the patients were classified into Shen-yin deficiency type and Shen-yang deficiency type, and Spleen (Pi)-supplementing, blood-activating and toxin-removing methods were given attention based on syndrome differentiation.

The commonly used drugs were as follows: Radix Rehmanniae (crude and prepared), Fructus Corni, Radix Polygoni multiflori, Fructus Psoraleae, Semen Cuscutae, Radix Moromdae Officinalis, Herba Cynomorii, and Herba Epimedii. Drugs for modification depending on syndrome differentiation were as follows: for patients with apparent Kidney-yin deficient syndrome, adding Fructus Morus, Fructus Ligustri lucidi, Rhizoma Polygonati, Fructus Lycii; for patients with apparent Kidney-yang deficient syndrome, adding Rhizoma Curculiginis, Herba Cistanches; for patients who also had Spleen-deficient syndrome, adding Radix Pseudostellariae, Rhizoma Atractylodes alba, and Rhizoma Dioscoreae; for patients dominant in blood-deficiency, adding Radix Astragali, Radix Angelicae sinensis, Radix Paeoniae, and Placenta Hominis; for patients with accompanying blood-stasis syndrome, adding Radix Salviae miltiorrhizae, Caulis Spatholobui, Herba Leonuri, and Rhizoma Chuanxiong; and for those also with heat-toxin syndrome, adding Rhizoma Smilacis Glabrae, Herba Taraxaci, Flos Lonicerae, and Fructus Forsythiae. The above drugs were given as one dose every day, decocted with water and taken in two parts in the