Bull Yamaguchi Med School 52(3-4):33-35, 2005

The Clinical Hematology at Yamaguchi Prefecture Central Hospital

Kenji Shinohara

Division of Hematology, Department of Medicine, Yamaguchi Prefectural Medical Center, 77 Ohsaki, Hofu, Yamaguchi 747-8511, Japan
(Received July 21, 2005)

Key words: aplastic anemia, leukemia, protein C deficiency, hemoglobinopathy

It is a great honor to receive the Sojinkai alumni Fujiu award.

When I came to this hospital in 1988, I felt that I might no longer be able to publish papers.

However, I tried to analyze each case that came before me. When I found interesting points, I tried to publish them as a case report or a letter to the editor, and to receive the criticism, for the purpose of teaching the rotating residents how to treat and analyze each patient and produce papers.

I once had thought in my university hospital life, that we could not treat the patients of severe aplastic anemia, before bone marrow transplantation became available. The pathogenesis of aplastic anemia was revealed by Neal Young of NIH as the damage to hematopoietic stem cells by increased cytotoxic T cells and increased γ interferon secretion. We found that the production of tumor necrosis factor α is also increased, and this cytokine may also damage hematopoietic stem cells.[1] This result was referred to in the "bible" hematology text book of Wintrobe and Williams. We also demonstrated that the TNF and FAS systems are also activated by demonstrating that soluble receptors are also increasedly produced.[2)4)] We think that these activated TNF and FAS systems may be the possible targets for inhibiting the injury to hematopietic stem cells. Endogenous production of hematopietic growth factors in aplastic anemia patients was inversely increased to the degree of damaged hematopoiesis, and the result suggested that the administration of recombinant hematopoietic grwoth factors might not be useful for the treatment of bone marrow failure.[5)6)] In myelodysplastic syndrome, which is thought to be closely related to aplastic anemia, mutation of N-Ras oncogene is frequently observed, however, the mutation was not observed in the patients of aplastic anemia, suggesting the different pathogenesis of these disorders.[7)] We demonstrated that viral infection could cause cytopenias; Epstein-Barr virus caused aplastic anemia,[8)] and also that parvovirus B19 infection caused thrombocytopenia.[9)] Recently we reported the first Japanese patient of pure red cell aplasia caused by the antibody to administered erythropoietin in a patient with chronic renal failure.[10)]

We successfully performed the allogeneic bone marrow transplantation in a patient of aplastic anemia. We also performed autologous bone marrow and peripheral blood stem cell transplation for hematological malignancies in more than 30 patients, and half of the patients are still alive without relapse. The patients of therapy-related myelodysplastic syndrome and leukemia are increasing. It is necessary to prevent or diagnose early the development of these patients. We experienced several cases of therapy-related leukemia with unique chromosomal translocations.[11)12)] There were offers from the other laboratories, and the novel partner

genes were identified at the breakpoints of chromosomes; MTG-16 with AML1,[13] and AF17q25 with MLL.[14]

For the chemotherapies for the acute leukemia of the aged or myelodysplastic syndrome, intensive chemotherapy is frequently untolerable and therapy related mortality is high. We developed combination chemotherapies including low doses of cytosine arabinoside (C), anthracycline (A) and granulocyte colony-stimulatin factor (G-CSF) with the aim of synchronizing the leukemic cells in the S-phase of the cell cycle and kill leukemic cells by S-phase specific anti-leukemic agents.[15] Later, this concept was developed and widely used as CAG therapy. Unfortunately we wrote in Japanese, and CAG was repored in English by an other author. It is important to write papers in English.

We previously reported a case of capillary leak syndrome caused by G-CSF administration.[16] It was later recognized as interstitial pneumonia causing acute respiratory distress syndrome.

We reported a case with skin necrosis at the injection site of α interferon in a patient of chronic myelogeneous leukemia.[17] Later the same effect was reported as the first reported adverse effect in the New England Journal of Medicine by an other author. We claimed that our case was reported earlier, and it was accepted and published in the journal.[18]

We reported the first Japanese patient of thrombotic thrombocytopenic purpura induced by ticlopidine,[19] and the case was referred in the review of the American Journal of Medicine.

We found a case of protein C, and the novel mutation of the gene was identified at the other laboratory, and added to the world database.[20]

We found a rare family case of Hb Hirosaki which was diagnosed by the specific gene mutation at an other laboratory.[21]

We published many case reports in the Yamaguchi Medical Journal in Japanese.

I have not studied on a single theme, and it is difficult to do so at a local hospital. However, it is possible to analyze the diagnosis and treatment of each patient case in detail. Molecular studies are necessary. However, they are impossible in the local hospital, however, yet they are possible in collaboration with other laboratories. I think we can perform clinical studies at hospitals outside of universities. It is needed these days.

Acknowledgement

I thank each professor of the third department of medicine (the late Toshio Kaneko, Yoshitomo Oka (presently at Tohoku University) and Yukio Tanizawa) for sending the residents continuously. I also thank the former chair Dr Daishiro Yuge and the present chair Dr Kensuke Esato of the hospital for supporting the clinical studies at this hospital.

References

1) Shinohara, K., Ayame, H., Tanaka, M., Matsuda, M., Ando, S. and Tajiri, M. : Increased production of tumor necrosis factor-α by peripheral blood mononuclear cells in patients with aplastic anemia. *Am. J. Hematol.,* **37** : 75-79, 1991.
2) Shinohara, K., Ayame, H., Yoshida, T. : Increased levels of soluble Fas antigen in the plasma of the patients with refractory anemia. *Int. J. Hematol.,* **65** : 413-414, 1997.
3) Shinohara, K., Takahashi, T., Nawata, R. and Oeda, E. : Decreased expression of the Fas ligand on peripheral blood mononuclear cells and undetectable levels of soluble Fas ligand in the serum of patients with aplastic anemia and myelodysplastic syndromes. *Am. J. Hematol.,* **62** : 124-125, 1999.
4) Shinohara, K., Muraki, K., Ota, I., Nawata, R., Oeda, E. and Takahashi, T. : Increased levels of soluble tumor necrosis factor receptors in patients with aplastic anemia and myelodyaplastic syndrome. *Am. J. Hematol.,* **65** : 326-327, 2000.
5) Yujiri, T. and Shinohara, K. : Fluctuation in serum cytokine levels in patient with cyclic neutropenia. *Am. J. Hematol.,* **39** : 144-145, 1992.
6) Shinohara, K., Oeda, E., Nomiyama, J., Inoue, H., Kamei, S., Tajiri, M., Ichikawa, T., Kuwaki, T. and Tachibana, T.: The levels of granulocyte colony-stimu-

lating factor in the plasma of the bone marrow aspirate in various hematological disorders. *Stem Cells,* **13** : 421-427, 1995.

7) Shinohara, K., Yujiri, T., Kamei, S., Ayame, H., Tanaka, M., Ando, S. and Tajiri, M. : Absence of point mutation of N-ras oncogene in bone marrow cells with aplastic anemia. *Int. J. Cell Cloning,* **10** : 94-98, 1992.

8) Inoue, H., Shinohara, K., Nomiyama, J. and Oeda, E. : Fatal aplastic anemia caused by Epstein-Barr virus infection after autologous bone marrow transplantation for non-Hodgkin malignant lymphoma. *Intern. Med.,* **33** : 303-307, 1994.

9) Oeda, E., Shinohara, K., Inoue, E. and Nomiyama, J. : A case of parvovirus B19 infection caused severe peripheral blood thrombocytopenia and persistent viremia. *Am. J. Hematol.,* **45** : 274-275, 1994.

10) Shinohara, K., Mitani, N., Miyazaki, M., Sakuragi, S., Matsuda, K., Ogawara, S., Saito, T., Kaneoka, H. and Ooji, T. : Pure red-cell aplasia caused by the antibody to recombinant erythropoietin-β, in a Japanese patient with chronic renal failure. *Am. J. Hematol.,* **78** : 15-20, 2005.

11) Takeda, K., Shinohara, K., Kameda, N. and Ariyoshi, K. : A case of therapy-related acute myeloblastic leukemia with t(16 ; 21) (q24 ; q22) after chemotherapy with DNA-topisomerase II inhibitors, etoposide and mitoxantrone and the alkylating agent, cyclophosphamide. *Int. J. Hematol.,* **67** : 179-186, 1998.

12) Nawata, R., Shinohara, K., Yamada, T., Takahashi, T., Katsuki, K., Takeda, K., Kameda, N., Ariyoshi, K., Ota, I. and Muraki, K.: Morphological and cytogenetic changes in therapy-related leukemia developed in a t(8 ; 21)-acute myeloid leukemia (M2) patient ; sequential cytogenetic and molecular analysis. *Int. J. Hematol.,* **71** : 353-358, 2000.

13) Gamou, T., Kitamura, E., Hosoda, F., Shimizu, K., Shinohara, K., Hayashi, Y., Nagase, T., Yokoyama, Y. and Ohki, M. : The partner gene of AML1 in t(16 ; 21) myeloid malignancies is a novel member of the MTG8 (ETO) family. *Blood,* **91** : 4028-4037, 1998.

14) Taki, T., Ohnishi, H., Shinohara, K., Sako, M., Bessho, F., Yanagisawa, M. and Hayashi, Y. : AF17q25, a putative septin family gene, fuses the MLL gene in acute myeloid leukemia with t(11 ; 17) (q23 ; q25). *Cancer Res.,* **59** : 4261-4265, 1999.

15) Oeda, E., Shinohara, K., Nomiyama, J. and Inoue, H. : The comination therapy with Ara-C and G-CSF in Hypoplastic leukemia and myelodysplastic syndrome (in Japanese). *Biotherapy,* **7** : 1729-1734, 1993.

16) Oeda, E., Shinohara, K., Kamei, S., Nomiyama, J. and Inoue, E. : Capillary leak syndrome likely the result of granulocyte colony-stimulating factor after high-dose chemotherapy. *Intern. Med.,* **33** : 115-119, 1994.

17) Oeda, E. and Shinohara, K. : Cutaneous necrosis caused by injection of alpha-interferon in a patient with chronic myelogeneous leukemia. *Am. J. Hematol.,* **44** : 213-214, 1993.

18) Shinohara, K.: More on interferon-induced cutaneous necrosis. *N. Engl. J. Med.,* **33** : 1222, 1995.

19) Ariyoshi, K., Shinohara, K. and Xu-Ruirong.: Thrombotic thrombocytopenic purpura caused by ticlopidine which was successfully treated by plasmapheresis. *Am. J. Hematol.,* **54** : 175-176, 1997.

20) Takahashi, T., Shinohara, K., Nawata, R., Wakiyama, M. and Hamasaki, N. : A novel mutation of protein C gene with a frameshift deletion of 3 base pair (3380AGG) in exon 6 in type 1 deficiency associated with arterial and venous thrombosis. *Am. J. Hematol.,* **62** : 260-261, 1999.

21) Tanaka, Y., Matsui, K., Matsuda, K., Shinohara, K. and Harano, K. : A family of Hb Hirosaki. *Int. J. Hematol.,* in press.