Available online at www.ujpronline.com
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

RESEARCH ARTICLE

A RETROSPECTIVE STUDY OF THE TREATMENT RESULTS OF 40 DIVERSE PATIENTS OF ANEMIA

George Zhu
University Hospital Leiden, The Netherlands.

Article Info:

Article History:
Received: 6 February 2021
Reviewed: 8 March 2021
Accepted: 11 April 2021
Published: 15 May 2021

Cite this article:
Zhu G. A retrospective study of the treatment results of 40 diverse patients of anemia. Universal Journal of Pharmaceutical Research 2021; 6(2):8-13.
https://doi.org/10.22270/ujpr.v6i2.562

***Address for Correspondence:**
Dr. George Zhu, University Hospital Leiden, The Netherlands.
E-mail: *sansan4240732@163.com*

Abstract

Background and objective: Anemia is clinical common event. There are many types of anemias, which included stem cell problems, vitamin deficiency, chronic diseases and drug antibody induced immune hemolytic anemia. In this study, a retrospective purpose was investigated to assess the clinical efficacy of treatment and their outcome.
Methods: Total 40 patients with different types of anemias were presented in the second affiliated hospital of central south University, China and my tumor institute during 1989-2019. The therapeutically design among those patients with anemias was setted to the various regimen according to diseases diagnoses.
Results: Total 23 patients achieved cure or complete remission (CR), with the exception of refractory cancers and uremic anemia. Iron supplement was provided in 5 iron deficiency anemia. One megaloblastic anemia produced an excellent response following the supplement of vitamin B_{12} and folic acid. 2 aplastic anemia obtained complete remission with the integrated protocol of methyltestosterone, adenine, leucogen, and levamisol. Steroid hormone (e.g. prednisone) mixed traditional medicine were occasionally promising benefit in a nephrotic syndrome and renal insufficiency. Among 2 cases with drug-induced immune hemolytic anemia (DIIHA), laboratory studies one patient's serum contained paracetamol-dependent antibody that in the presence of paracetamol, agglutinated *in-vitro* with "O" red cells with or without complement. Drug antibody titer was 1:4 positive.
Conclusions: Immune hemolysis was mediated by both the immune complex and uptake of drugs, whereas hemolysis induced by another native herb was caused by absorption of the drug only. In addition, with respect to anemia induced by malignancies, the molecular genomic regulation of retinoic acid in APL has been elucidated. Therefore, promoting effective prevention and/or early preventive treatment of anemia is our concern.
Keywords: Anemia drug induced immune hemolytic anemia (DIIHA) iron, folate and vitamin B_{12} megaloblastic anemia, prevention and treatment.

INTRODUCTION

Anemia is the common blood condition in clinical. Anemia is defined as the condition of a reduced number of circulating erythrocytes and/or a reduced concentration of hemoglobin in peripheral blood[1]. The anemias fall into two major categories: (1). those primarily caused by deficient erythropoiesis and (2). Those primarily caused by accelerated destruction of erythrocytes[2]. The former associates with a normal iron diet (about 17 mg of iron supplies per day) and iron loss (eg. gastrointestinal bleeding). Normal maturation of erythroid precursors depend on two classes of hematopoietic factors, the vitamin B_{12} coenzymes and the folates. Folates act as a growth factor by regulating the transfer of single carbon units in the metabolic processes. In chemical structure of vitamin B_{12}, methylcobalamin dependent pathway of methionine synthesis serves primarily as a means for converting N5-methytetrahydrofolate to tetrahydrofolate[2]. A deficiency of vitamin B_{12} and folate, therefore, resulting in deficient DNA synthesis of red cell and other hematopoietic precursors, manifested as megaloblastic dyspoiesis[2]. The recent novelty progress is put into the field of drug antibody-induced immune hemolytic anemia (DIIHA)[3,4]. In addition, many hormones such as erythropoietin participate in the regulation of erythropoiesis. Hormones involve enzyme and protein synthesis, which also affect synthesis of hemoglobin and production of red cells. The uremic anemia is the case in this field. There are many types of anemia. Conditions associated with the

causes of anemia include: bone marrow and stem cell problems (such as aplastic anemia, thalassemia), iron deficiency anemia (IDA), anemia due to vitamin deficiency, especially vitamin B_{12} or folic acid. Anemia is also associated with other chronic diseases, such as advanced kidney failure or cancer. One of the most famous reports is in the field of immune hemolytic anemia induced by antibodies. This paper will attempt to place in a retrospective survey of 40 different types of anemia outcomes in this group.

Total 40 anemias were included in the study during 1989-2019. All patients were in progressive at hospital. The sex ratio of male: female was 25:15 respectively. Among age distribution, it was ranging from 2 to 75 years. The clinical diagnosis in a broad variety of anemias consisted of iron deficiency anemia (IDA) 5 cases; aplastic anemia(AA) 2; megaloblastic anemia(MA) 1; idiopathic thrombocytopenic purpura (ITP) accompanied by severe anemia 1; malarial anemia 1;uremic anemia(UA) 2; drug-induced immune hemolytic anemia (DIIHA) 2 [1 case following paracetamol-induced, another case following herbs *Origanum vulgare* (wild mint)-induced];26 anemias whom caused by various tumor were shown in Table 2. As ethical approval is an integral part of the research process, ethical permission details of this study should be clearly indicated.

The treatment regimen varied among different types of anemias. The criteria of complete remission (CR) and/or partial remission (PR) in cancers is according to the rules where physicians have in common with in clinics. Complete remission (CR): there was no tumor or tumor complete regressed in patients for at least 1 month; Partial remission (PR): the tumor decreased by more than 50% in patients for at least 1 month. Disease progression: the tumor increased by more than 25% in patients, or new lesions emerged. The efficacy was evaluated according to the survival time from the day when patients were at onset. The clinical data for 2 cases of DIIHA were previously described.

Table 1: Patients characteristics.

Sex	Age	Hb(g/l)	WBC(x109/l)	Platelets (x109/l)	Diagnosis	Protocol	Outcome	No
M3, F2	32-50	30─50	3.5 – 5.6	62	IDA*	iron	cure	5
M	43	59	2.6	11.8	MA	VB12, folic acid, TCM	cure	1
M2	16,19	40, 90	2.8, 4.1	3.0, 20	AA	MT, leucogen, levamisol	cure	2
F	35	46.9	6.5	34 ~ 80	ITP	pred, TCM	unknown	1
M2	34,25	51,63	14.7, 5.7	208, 184	DIIHA	stop drug	cure	2
F2	63	79	5.1	167	UA	TCM,pred	1 CR	2

Table 2: Patients with anemias caused by malignant tumors.

Sex	Age	Hb(g/l)	WBC(x109/l)	Plateles (x109/l)	Diagnosis	Protocol	Outcome	No
M3, F3	2-20	37─60	4.2 – 11.1	2.8 – 10.9	AML	DA, HA	3PR	6
M	31	53	3.4	2.4	APL	RA, H, TCM	CR	1
M1, F1	33,60	70, 80	160, 233	332, 375	CML	Busulfan	CR	2
M	43	75	80.0	60.0	CML crisis	RA, H, pred	PR	1
M	58	87	123	131	CLL	chlorambucil	CR	1
F	62	94	4.8	154	MM	TCM, pred, thalidomide	CR	1
M	20	40	2.0	4.2	ALL	VP	PR	1
M1, F1	43, 35	59, 40	2.6 – 6.6	11.8	MDS	VB_{12},folate,TCM	1CR,1progression	2
M2, F2	35-50	95	10.3	263	gastric cancer	FAM, FMC, anti-tumor tab.	2 short CR,1cure,1PR	4
M4, F2	24-75	58-39	9.7 – 1.45	31.0 – 38	others**	TCM,5─Fu	1 CR	7

Note: **others included: metastatic lymph node adenocarcinoma 1 case, Hb 58g/l; lymphadenopathy and metastatic bone tumor 1; nasopharyngeal carcinoma 2; colon cancer 1; bladder cancer 1; and advanced liver cirhosis with gastric hemorrhage 1 case, Hb 39 g/l, hemocrit (HCT) 13.8%, RBC $2.02x10^{12}$/l, the patient transferred into another hospital. M: male, F: female. ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; CML: chronic myeloid leukemia; CML crisis: CML with blast crisis; CLL: chronic lymphocytic leukemia; MM: multiple myeloma. TCM: traditional medicine. Pred: prednisone. VP: vincristine, prednisone.

RESULTS

Anemia treatment will depend on the different types of anemias. In the current study, 23 patients achieved cure or complete remission (CR) (9 CR and 14 cure) through different regimen of integrated western and traditional medicine. During drug administration, oral iron preparation is available in 5 patients with iron deficiency anemia (IDA) or IDA following gastric ulcer hemorrhage. A significant increase in hemoglobin can be obtained in response to iron therapy. One patient with megaloblastic anemia produced an excellent response following the supplement of vitamin B_{12} and folic acid. Steroid hormones (e.g. prednisone) and especially traditional medicine produced complete remission in one nephrotic syndrome and renal insufficiency (Table 1). Regarding malignant tumors, a short CR was achieved by the use of combination regimen of FAM or FMC (5-Fu, Ara-C, mitomycin C or CTX), and cantharidin in 3 advanced gastric cancers. One of them was a long-term survivor for 6 years. Partial remission (PR) was obtained by DA regimen (daunorubicin 40 mg/m^{2}x3 days, Ara-C 200 mg/m^{2}x 4 days) in 1 case with M1 type in another hospital and HA combination chemotherapy (homoharringtonine 4 mg/m^{2}x3 days, Ara-C 50 mg

intramuscular injection, twice daily for 5 days) in a case with M2 type of acute myeloid leukemia. A CR was obtained in an acute promyelocytic leukemia (APL) through retinoic acid and one course of 5 days of 1 mg homoharringtonine (H) intravenously and traditional medicine one month duration. He was a 20 months of survivor. A 62-year-old woman with chronic myelocytic leukemia achieved CR after busulfan and antibiotics regimen. She was a survivor for near 8 years (Table 2). Drug-induced immune hemolytic anemia (DIIHA) is a rare cytopenia. In current study, DIIHA is considered in 2 patients. A 25-year-old patient with paracetamol-dependent antibodies reactive by immune complex type and drug adsorption mechanisms. Another herbs *Origanum vulgare* (wild mint)- treated antibody determination, the patient's serum results in agglutination and hemolysis of drug-treated "O" RBCs (RBCs coated with herbal wild mint) with coombs antiserum IgG at 37℃, indicating a drug adsorption mechanism. Drug antibody titer was 1:4 positive. When washing drug-coated RBCs with saline solution repeatedly, it was found to still appear a coombs test positive. Once DIIHA is considered, management included the appropriate serologic determination, immediate discontinuation of the implicated drugs and corticosteroids to ameliorate DIIHA symptoms and reduced the drug antibody.

Case 1: On November 11, 1985, a 25-year-old man was admitted to the second affiliated hospital of Central South University, China due to his anemia and persistent jaundice. After careful inquiry, in March 1985 and July 1985 respectively, he had a history of 4 (total 8 capsules) Ka Huang Min capsules (paracetamol, caffein, and artificial cow-bezoar and chlorphenamine maleate capsules). In 1984, he once had a past history of taking 6 capsules Ka Huang Min drug. And one month later, he developed immune hemolytic anemia. At physical examination showed chronic anemia, mild icteric sclera. T 37.3℃, P 92/min, BP 100/70 mmHg. There was no bleeding and lymph-adenopathy. A grade II systolic murmur was audible at the apex. The lower border of his liver was paplpable 1.5 cm below the right costal margin, and the spleen edge could be felt 3 cm below the left costal margin. Laboratory data: Hb 63 g/l, WBC 5.7 x10^9/l, leukocyte differential count: segmented neutrophils 48%, lymphocytes 42%, monocytes 6%, eosinophils 4%. Platelets 184x10^9/l. Reticulocyte count was 10.0%. Urine analysis: protein trace, urobilinogen (+), urine bilirubin (–). Icteric index (II) was 18 units. Serum AST was normal. The serum total bilirubin was 29.07 μmol/l. The serum haptoglobin level was 505 mg/l. The serum albumin (ALB) 44.8 g/l, globulin 30.8 g/l. HbA2 was 5.1~5.57%, HbF 8.23~9.05%. Hemoglobin electrophoresis showed normal electrophoretic pattern. Ham test, sucrose hemolysis test, methemoglobin reduction test, and isopropanol test were all negative. Direct antiglobulin test (DAT) (Coombs) was 1:4 positive. Cold agglutinin test was 1:16. Bone marrow was hypercellularity, M: E=0.7:1, 51.6% erythroid, orthochromic normoblasts occupied the predominant cells of erythroid, and many anisocytosis and poikilocytosis. Erythrocyte osmotic fragility test (ROFT): at initial hemolysis: patient 0.40%, control 0.48%; at complete hemolysis: patient 0.24%, control 0.28%. The results of decreased ROFT and increased HbA2**,** HbF level indicated the diagnosis of mild β thalassemia trait.

To confirm paracetamol-induced DIIHA, the solution of Ka Huang Min capsules containing all four ingredients were performed using serological tests (Table 3). The results implicated that paracetamol - dependent hemolysis was via both immune complex and drug adsorption. If there was autoantibodies (DAT titer 1:4), which remained testable. In December, 1985, Hb reached to 92 g/l, and reticulocyte count was declined to 2.6%.

Case 2: On September 4, 1985, a 34 year-old man was admitted to the second affiliated hospital of Central South University, China due to his headache, pallor and hemoglobinuria for 4 days. On August 28, 1985, the patient felt sore and ache all over, and specially a pain in his right thigh. He had taken a daily dose of 3000ml traditional decoction. Traditional medicine included kudzuvine root (*Radix puerariae*), *Serissa japonica* (*Serissa serissoides*), and *Origanum vulgare* (wild mint).

Table 3: Reactivity of patient' serum with normal untreated "O" RBCs in various reagent conditions.

Test reagent mixture	IAT
Patient's serum + O red cells coated with Ka Huang Min solution*	+
Patient's serum + O red cells coated with caffein	—
Patient's serum + O red cells coated with cow-bezoar	—
Patient's serum + O red cells coated with chlorphenamine	—
Patient's serum + Ka Huang Min solution* + untreated O red cells	+
Patient's serum + other drugs** + untreated O red cells	—
Normal serum + O red cells coated with Ka Huang Min solution	—
Normal serum + Ka Huang Min solution* + untreated O red cells	—

Note: *Ka Huang Min solution containing four ingredients of paracetamol, caffein, artificial cow-bezoar,and chlorphenemine. **Antibody tests including only caffein, cow- bezoar or chlorphenamine respectively.

After 4 days, an episode of 4 days of significant hemoglobinuria (soy urine) was noted. On September 2, 1985, he developed icteric skin and sclera, and his temperature reached to 38℃. His initial hemoglobin level was 50 g/l. He was the suspect of "hepatitis" in a local country hospital, and subsequently as anemia cause, transferred to our hospital. He had no past history of tuberculosis. Upon physical evaluation: T 38.2℃, P 96/min, R 32/min, BP 120/60 mmHg, icteric skin, sclera and mucous membranes. There was no abnormal in his heart and lung. The liver edge could be palpable 1.5 cm below the right costal margin and no

spleenomegaly. Laboratory evaluation: Hb 51 g/l, WBC 14.7 x10^9/l, leukocyte differential count: segmented neutrophils 81%, lymphocytes 16%, monocytes 2%, eosinophils 1%. Platelets 208 x 10^9/l. Urine samples were negative for proteins. Serum BUN 9.7 mg/dl. The serum albumin (ALB) 3.56 g/dl, and globulin (GLB) 3.21 g/dl. Serum immunoglobulin (Ig) detection: IgG 1185.3 mg%, IgA 264.9 mg%, IgM 197.5 mg%. Serum HBsAg was negative. Direct antiglobulin test (DAT) (Coombs') was negative. Bone marrow was cellularity. Bone marrow differential count: 48% myeloid, 42.6% erythroid, approximately 31.0% of predominant cells was orthochromic normoblasts, and many anisocytosis and poikilocytosis. To confirm the drug-induced immune hemolytic anemia (DIIHA), the drug-related serologic tests performed according to standard methods (Table 4). The titer of drug antibody was 1:4. After discontinuation of offending herbs, on September 5,1985, Hb was 75 g/l, reticulocytosis 24.6% (control:0.5-1.5%); On September 9, 1985, Hb reached to 87 g/l, WBC 6.5x10^9/l, platelets 109 x10^9/l, reticulocytosis 28.1%; At discharging from hospital, on September 18,1985, Hb was 95 g/l, reticulocyte count was 5.6%. After the follow up, the patient reached essentially near normal hematologic levels.

Table 4: Reactivity of patient's serum with normal untreated or papain-treated O RBC's in various reagent conditions.

Test reagent mixture	IAT	
	Agglutination	Hemolysis
Patient's serum + drugs* + O RBCs	—	—
Patient's serum + drugs* + complement** + O RBCs	—	—
Patient's serum + *Kudzuvine root*- coated RBCs	—	—
Patient's serum + *Origanum vulgare*- coated RBCs	+ (titer 1:4)	+
Patient's serum + *Serissa serissoides*-coated RBCs	—	—
Normal serum + *Origanum vulgare*- coated RBCs	—	—

Note: *Antibody tests with three kinds of herbs (see above) respectively. Experimental methods according to Prof. Garratty's and Prof. Lin's further modification. **normal guinea pig serum as a complement source. IAT: indirect antiglobulin test

Case 3: On February 4, 1990, a 16 year-old boy was the chief complaint of sudden drops of blood from nostril, and intermittent up to about 5 hours. On February 15, 1990, an episode of repeat epistasis occurred for 2 hours duration. The prescribed drugs vitamin C and ubiquinone (CoQ) revealed ineffective to his hemostasis. Since the winter of 1989, the patient presented the symptoms of fatigue and progressive weakness. On February 24, 1990, the patient was advised to be further examination in a local country hospital. Hemogram: Hb 40-53 g/l, WBC 2.8-4.0 x 10^9/l, leukocyte differentiate count: 26-33% segmented neutrophils, 67-74% lymphocytes. Platelets count was 30 x10^9/l. Bone marrow was the definite diagnosis of aplastic anemia on March 6, 1990. At that time, the patient occasionally passed out, and he catched a persistent fever over 39℃. After grinding and drink with *Rhinoceros horn* solution daily, the processed plan was considered the combination of methyl-testosterone (MT, 30 mg/day), leucogen, vitamin B4(adenine) and Batil, and levamisole. Remission was obtained following 4 months treatment duration. An induction of breast tumours was unexpectively uncovered by the use of 6+ months of methyltestosterone treatment, and tumour was progressive regressed after stopping this drug for four months.

Case 4: On April 14, 1999, a 50-year-old woman was admitted to hospital due to her chronic anemia and recurrent abdominal pain for more than half a year. In September, 1998, the patient presented a unexplained dull pain in the epigastrium, accompanied with acid regurgitation and belching. No nausea and vomiting were noted. Physical examination revealed anemia. There was no obvious tenderness around the umbilicus. A 10x 8cm^2 harden mass was palpable in the abdomen, with a unsmooth surface and an indistinct surrounding. Gastroscope showed an advanced gastric adeno carcinoma, complicated with hepatic metastasis. Treatment consisted of the combination regimen of daily 250 mg 5-Fu and 1~3 mg/day of homoharringtonine for 10 days, in conjunction with intravenous cinobufacine and oral demethyl cantharidin. Afterwards, combination chemotherapy was intermittent to be given according to patient condition. On May 18, 1999, she obtained a short CR. She was continued to the prescription of traditional medicine or 5-Fu solution mixed the decoction of traditional medicine.

Case 5: On October 16, 2003, a 31 − year-old man was the chief of his pallor and fever for 15 days. On admission, physical examination showed a marked anemia and hepatomegaly. Persistent fever reached to 39℃. Chest X-ray showed small amount of hydrothorax. Liver CT scan demonstrated a 7.0x4.5 cm^2 mass which was considered as secondary hepatic tumor. Serum AFP was negative. Laboratory data: hemoglobin concentration (Hb) was 53 g/l, white blood cells (WBC) count was 3.4x10^9/l, leukocyte differential count in blood smear: 20% promyelocytes. The platelet count was 2.4x10^9/l. Bone marrow aspiration revealed normal cellularity. Bone marrow differential count showed 77% promyelocytes. Treatment consisted of 80 mg/day of retinoic acid (RA) and 1 mg/day of homoharringtonine (H) intravenously for 5 days. His high fever was declined to normal following small dose of dexamethasone and traditional medicine. On November 20, 2003, repeated bone marrow smear showed only 3.5% myeloid blast and promyelocytes. On the routine peripheral blood smear uncovered no

immature myeloid cells. Hemogram: Hb 102-108 g/l, WBC 7.7-5.0x10^9/l, platelets 229x10^9/l.

CR was obtained after one month period of RA, chemotherapy and traditional medicine. On June 5, 2005, he died of APL relapse (94% blasts and promyelocytes in peripheral blood and in bone marrow). The repeated liver scan found the complete regression of his liver tumor albeit the recurrence of his leukemia.

Case 6: On April 9, 2006, a 43 year-old man was admitted to the hospital because of dizziness fatigue and progressive weakness for more than half a year. At a routine physical examination, there was revealed a marked anemia. Hemogram: Hb 59 g/l (control:131-172 g/l), RBC 1.90 x10^{12}/l (control: 4.0-5.5 x10^{12}/l), WBC 2.6 x10^9/l, platelet count 11.8 x10^9/l. Urinalysis showed bilirubinuria. Bone marrow aspirates revealed normal cellularity. Bone marrow differential count: 48.4% myeloid, 30.4% erythroid, 2.4% basophilic megaloblasts, 6.0% polychromatophilic megaloblasts, and 2.0% orthochromic megaloblasts. The diagnosis of refractory anemia or pernicious anemia was made. Treatment consisted of a regimen of full doses of hematopoietic stimulating agents vitamin B_{12} injection and the supplement of folic acid, and in conjunction with traditional medicine and Lujiaobuxue granules ingredients. Cure was obtained three months later. Traditional medicine included: *Angelica sinensis, Radices rehmanniae, Codonopsis pilosula, Astragalus membranaceus, Lycium barbarum* (wolf berry), *Semen coiois,* Stiff silkworm, *Daizheshi* (processed Haematite), *Ophiopogon japonicus*, Donkey-hide gelatin, *Poria cocos*, orange peel, licorice (glycyrhiza). He was well until on July 27, 2011 while an attack of his marked anemia relapse was admitted to hospital once again. Routine hemogram: Hb 66 g/l, hematocrit reading 25.0% cell volume (control: 38-50.8%), MCH 30.3pg (27.8-33.8 pg), MCHC 265 g/l (320-355 g/l), RBC 2.19 x10^{12}/l(4.09-5.74 x10^{12}/l), WBC 2.3x10^9/l(4-10 x10^9/l), platelet 152 x10^9/l(100-300 x10^9/l). Faeces for occult blood test (OBT) was weak positive. During the follow up of 9 years, in August, 2020, he had his third relapse of disease. Serum iron (serum Fe) was 10.3μmol/l (control: 10.6~36.7 μmol/l). Serum ferritin assay was 271.57-278.51 ng/l (control: 21.8~274.66 ng/l). Serum vitamin B_{12} was 83 pg/ml (control: 187.0~883.0 pg/ml). Serum folic acid was 7.6ng/ml (control: 3.1~20.5ng/ml). After a series of treatment with hematopoietic stimulating agents and traditional medicine, he remained complete remission (CR) now.

Case 7: A 62-year-old woman was admitted to the hospital due to her progressive weakness and fatigue, recurrent episodes of cough, and blood-tinged sputum for 1^+ month. Physical examination revealed a pale,tired, elderly person. T 36.5℃, P 98/min, R 24/min, BP 115/68mmHg. On lung CT scan showed a mass shadow at her right middle lobe, which was considered as pulmonary infection or suspected tumour. In addition, the patient was also found to have her bilateral pleural effusion. The patient had a past history of old myocardial infarction, and frequent ventricular premature beats. Routine blood hemogram: Hb 94 g/l, RBC 3.13 x10^{12}/l, WBC 4.8 x10^9/l, platelets 154 x10^9/l. Erythrocyte sedimentation rate (ESR) 125mm in 1 hour. Serum ALT was 92.4 μ/l. Serum AST was 120.7 μ/l. Serum HBsAg was negative. The laboratory finding was typical of multiple myeloma. Bone marrow showed hypercellularity. Bone marrow differential count: myeloid 41%, erythroid 19.5%, plasmablasts 1.5%, and plasmacytes 26%. Serum albumin (ALB) was 25.8~29.6 g/l, globulin(GLB) was 50.3~54.8 g/l. Traditional medicine consisted of *Vinca rosea, Astragalus membanaceus Bunge, Ophiopogon japonicas, Asparagus cochinchinensis, Angelica sinensis, Poria cocos, Coix lacryma jobi L. var.ma-yuen, Solanum nigrum L, Houttuynia cordata, Scutellaria barbata d.don* and *Oldenlandia diffusa roxb.* In the chest X-ray the disappearance of lung mass shadow and her hydrothorax were noted following traditional medicine treatment one month later.

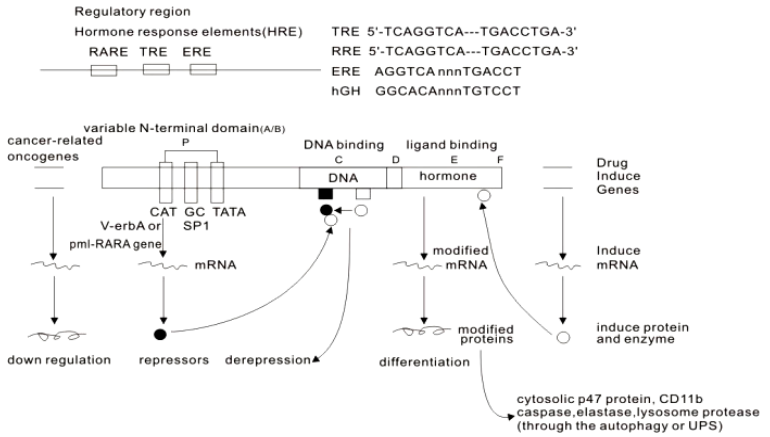

Figure 1: Molecular model of the gene regulation of retinoic acid (RA).

On April 17 and May 27, 2011 respectively, repeat peripheral blood studies revealed Hb 112～118 g/l, RBC 3.46(3.5~5.5) x10^{12}/l, WBC 4.93 x10^9/l, platelets 83 x10^9/l. Serum ALB 34.7 g/l(35~55 g/l), GLB 47.4 g/l (control:15~35 g/l). CR was obtained after additional prednisone and low-dose thalidomide. During the follow up of 3.5 years, she was remained CR.

DISCUSSION

In current study, a series of the long follow up of 40 different types of anemias were reported. Until now, about 130 drugs in DIIHA have been incriminated. In drug-dependent antibody formation, the most accepted idea involves covalent binding of the drug to erythrocyte membrane, creating a neoantigen composed of membrane and drug. An antibody (usually IgG) can be created against the drug, which then binds to the drug-coated erythrocytes and is subsequently activate complement, and cause acute hemolysis[3-8]. Drug-dependent antibody formation is most commonly caused by penicillin, peracillin, along with cefotetan and ceftriaxone[3-8]. We reported 2 patients with penicillin- induced DIIHA previously (Lin zhusan, Zhu yuejun, Zhang guangsheng, *et al*, 1984, data not shown)[9-15]. One 16-year-old boy was identified his penicillin antibody dependent hemolysis, which was mediated by immune complex type and drug adsorption. In immune complex type detection, the drug antibody titer reached to 1:512. Another 40-year-old woman with DIIHA was mediated by the drug-adsorption only. As a novel retinoic acid (RA) to APL treatment, this specific APL harboring oncogenic pml/ RARa fusion[16-20].

CONCLUSIONS

This oncogenic receptor derivative pml/RARa fusion act as a constitutive repressor of RAR and retinoic acid signaling, inducing differentiation blockade at promyelocytic stage, whereas pharmacologic retinoic acid (ATRA or cis RA) can bind to oncogenic pml/RARa, then relieve the blockage of pml/RARA repression (also derepression), and subsequently oncogenic pml/RARa degradation via autophagy/UPS proteosome system, immature prom-yelocytes toward maturation. Finally, APL patients obtained complete remission (CR). Therefore, it cannot be illustrated that the drug retinoic acids stimulate (bind to) a pml/RARa oncogene. This molecular model is first described in eukaryotes.

ACKNOWLEDGEMENTS

Author is thankful for the University Hospital Leiden, The Netherlands to provide necessary facilities for this work.

AUTHOR'S CONTRIBUTION

Zhu G: Writing original draft, review, literature survey, editing, methodology, data curation.

DATA AVAILABILITY

Data will be made available on reasonable request.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Maile JB. Anemia: pathophysiology, pathogenesis, and classification. In Maile JB ed: Hematology. Fifth Edition. The CV mosby company, Saint Louis, Missouri,1977:433 - 480
2. Beck WS. Megaloblastic anemias I. vitamin B_{12} deficiency. 2nd edition. The MIT press, Cambridge, Massachusetts, and London. 1977:69-100.
3. Petz LD. Immunologic reactions of human to cephalosporins. Postgrad Med J 1971; 47:64-69.
4. Petz LD, Garratty G. Immune hemolytic anemia, 2nd edition. Philadelphia: Churchill Livingstone 2004:261-317.
5. Arndt PA, Garratty G. Cross-reactivity of cefotetan and ceftriaxone antibodies, associated with hemolytic anemias, with other cephalosporins and penicillin. Am J Clin Pathol 2002; 118:256-262. *https://doi.org/10.1309/JFJE-VUKN-221T-G6EV*
6. Garratty G. Drug-induced immune hemolytic anemia. Hematology 2009; 73-79. *https://doi.org/10.1182/asheducation-2009.1.73*
7. Arndt PA, Leger RM, Garratty G. Serologic characteristics of ceftriaxone antibodies in 25 patients with drug-induced immune hemolytic anemia. Transfusion 2012; 52(3): 602-612. *https://doi.org/10.1111/j.1537-2995.2011.03321.x*
8. Renard D, Rosselet A. Drug-induced hemolytic anemia: phamacological aspects. Transfusion Clinique et Biologique 2017; 24:110-114. *https://doi.org/10.1016/j.tracli.2017.05.013*
9. Storb R, Thomas ED, Weiden PL, *et al*. Aplastic anemia treated by allogeneic bone marrow transplantation: a report on 49 new cases from Seattle. Blood 1976; 48(6):817-841.
10. Deeg HJ, Leisenring W, Storb R, *et al*. Long-term outcome after marrow transplantation for severe aplastic anemia. Blood 1998; 91(10):3637-45. *https://doi.org/10.1182/blood.V91.10.3637*
11. Zhu G. Oncogenic receptor hypothesis (1989-91). VOA (Voice of America) 1992; 12:31. *https://doi.org/10.19080/JETR.2019.04.555643*
12. Zhu G. A further study of patients with advanced cancer after chemotherapy with traditional medicine. The J Crit Car Med 2007; 2(11):618- 623
13. Zhu G. Five to ten years survivors of patients with advanced cancers after chemotherapy with traditional medicine. The J Crit Care Med 2009,4(9):512-519 (EBSCO).
14. Zhu G. Use of chemotgerapy and traditional medicine for advanced cancers: A retrospective study of 68 patients (1993~2010). JCCM 2010; 5(6):343-350 (EBSCO).
15. Zhu G, Mische SE, Seigneres B. Novel treatment of acute promyelocytic leukemia: As_2O_3, retionic acid and retinoid pharmacology. Curr Pharm Biotchnol 2013; 14(9):849 − 858. *https://doi.org/10.2174/1389201015666140113095812*
16. Zhu G, Saboor-Yaraghi AA, Yarden Y, Santos J, Neil JC. Downregulating oncogenic receptor: from bench to clinic. Hematol Med Oncol 2016; 1(1):30-40. *https://doi.org/10.15761/HMO.1000106*
17. Zhu G, Musumeci F, Byrne, Gupta D, Gupta E. Targeting oncogenic receptor, currently the standard of care. Clin Trails Pathol Case Studi 2017; 2(2):75-90.
18. Zhu G, Ali Al-kaf GA. Vitamin A, retinoic acid and tamibarotene, a front toward its advances: A review. Universal J Pharm Res 2018; 3(6):38-48. *https://doi.org/10.22270/ujpr.v3i6.215*
19. Zhu G. Vitamin A and its derivatives– retinoic acid and retinoid pharmacology. Am J Biomed Sci Res 2019; 3(2):162-177. *https://doi.org/10.34297/AJBSR.2019.03.000656*
20. Zhu G. APL: retinoic acid and retinoid pharmacology, breakthrough trials today. J Endocrinol Thyroid Res 2019; 4(4). *https://doi.org/10.19080/JETR.2019.04.555643*