

How I Treat Anemia

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Abstract

Anemia is clinical common event. In this study, a retrospective survey of 30 different types of anemias will attempt to place in proper interpretative review for their treatment outcome. By using comprehensive treatment regimen according to patients' condition, 20 patients obtained cure or complete remission (CR). Iron supplement was provided in 5 iron deficiency anemia. One megaloblastic anemia required the prescribed the supplement of vitamin B12 or folate deficiency. Steroid hormone (e.g. prednisone) mixed traditional medicine were occasionally promising benefits in a nephrotic syndrome and renal insufficiency. Among 2 cases with drug-induced immune hemolytic anemia (DIIHA), laboratory studies a patient's serum contained paracetamol-dependent antibody that agglutinated *in vitro* with "O" red cells with or without complement. The reactive mechanism was attributed to both immune complex type and drug-adsorption, whereas another herb *Origanum vulgare*- induced hemolysis secondary to drug adsorption only. In addition, regarding anemia caused by malignant tumours, the molecular genetic regulation of retinoic acid in acute promyelocytic leukemia (APL) has been further illustrated (see figure in full text). Therefore, to strength the active prevention and/or early interceptive treatment of anemia is our care.

Keywords: Anemia; Iron; Vitamin B12 and Folate; Drug Induced Immune Hemolytic Anemia (DIIHA); Prevention and Treatment

Introduction

Anemia is the common blood condition in clinical. Anemia define the condition in which there is a reduced number of circulating erythrocytes and a smaller than normal hematocrit or a reduced concentration of hemoglobin in peripheral blood. Many hormones, in addition to erythropoietin, participate in the regulation of erythropoiesis. Hormones that affect enzyme and protein synthesis also affect synthesis of hemoglobin and production of red cells. The characteristic anemia of hypothyroidism is normochromic-normocytic, mild to moderate anemia.

There are many types of anemia. Condition associated with the causes of anemia include: bone marrow and stem cell problems (e.g. aplastic anemia, thalassemia), iron-deficiency anemia (IDA), Vitamin deficiency anemia specifically vitamin B12 or folate. Anemia also linked to other chronic diseases, such as advanced kidney failure or cancer. One of the most remarkable reports is in the field of drug antibody-induced immune hemolytic anemia. In this study, a retrospective study of 30 anemias was presented as the following.

Material and Methods

30 animas were included in the study during 1989 - 2012. All patients were in progressive when they were hospital. The sex ratio of male:female was 17:13 respectively. Among age distribution, it was ranging from 4 to 75 years. The clinical diagnosis in a broad variety

of anemias included: iron deficiency anemia 1 case, Hb 49 g/l; gastric ulcer hemorrhage complicated with iron deficiency anemia 4 cases, Hb 30 - 50 g/l; megaloblastic anemia 1, Hb 59 g/l; aplastic anemia 2, Hb 40 - 90 g/l; idiopathic thrombocytopenic purpura (ITP) complicated with severe anemia 1, Hb 47 - 55 g/l; malarial anemia 1; drug-induced immune hemolytic anemia (DIIHA) 2 [1 case following paracetamol-induced, Hb 63 g/l, another case following herbs *Origanum vulgare* (wild mint) -induced, Hb 51 g/l]; uremic anemia 2, Hb 79 g/l; 16 anemias caused by various tumors: hematologic malignancies (ALL 1, Hb 55 g/l; AML 3, Hb 37 - 60 g/l; APL 1, Hb 53 - 59 g/l; CML 2, Hb 70 - 80 g/l; CML with blast crisis 1, Hb 75 g/l; CLL 1, Hb 87 g/l; metastatic lymph node adenocarcinoma 1, Hb 58 g/l). nasopharyngeal carcinoma 1; myelodysplasia (MDS) 2, Hb 40 - 65 g/l; gastric cancer 3 cases. The treatment regimen varied among different types of anemias. 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.

Results

Anemia treatment will depend on the different types of anemias. The remaining patients achieved 8 cases with complete remission or 12 cured through different regimen of integrated western and traditional medicine, with the exception of malignant cancers, uremic anemia and one patient with ITP transferred to another hospital.

During the schedule of drug administration, many preparations of oral iron are available in 5 patients with iron deficiency anemia (IDA) or IDA following gastric ulcer hemorrhage. A significant increase in hemoglobin can be gained by observing the response to adequate iron therapy. One patient with megaloblastic anemia often required the supplement of vitamin B12 and folic acid, which produced an excellent response. Steroid hormones (e.g. prednisone) and especially traditional medicine produced complete remission in one nephrotic syndrome and renal insufficiency.

As to the patients' anemias caused by 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.

In view of the types of hematological anemias, partial remission was conducted by DA regimen (daunorubicin 40 mg/m² x 3 days, Ara-C 200 mg/m² x 4 days) in 1 case with M1 type in another hospital and HA combination chemotherapy (homoharringtonine 4 mg/m² x 3 days, Ara-C 50 mg intramuscular injection, twice daily for 5 days) in a case with M2 type acute myeloid leukemia. An acute promyelocytic leukemia (APL) obtained CR via retinoic acid in conjunction with 5 days of 1 mg homoharringtonine intravenously and traditional medicine one-month duration. He was 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

Drug-induced immune hemolytic anemia (DIIHA) is a rare cytopenia. DIIHA is considered in 2 patient samples. A 25-year-old patient with paracetamol- dependent antibodies reactive by immune complex type and drug adsorption mechanisms. The direct antiglobulin test was 1:4 titer positive with polyspecific antiglobulin reagent. The patient's serum contained an antibody that, in the presence of paracetamol, results in agglutination of papain-treated "O" type of RBCs with complement. The serum also agglutinated paracetamol-coated RBC cells at 37°C (drug- adsorption). Another herbs *Origanum vulgare* (wild mint)- dependent antibody determination, the patient's serum results in agglutination and hemolysis of drug-treated "O" RBCs (RBCs coated with herb wild mint) with coombs antiserum IgG at 37°C, 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 Report

Case 1: On November 11, 1985, a 25-year-old man was admitted to hospital 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, caffeine, 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°C, P 92/min, BP 100/70 mmHg. There was no bleeding and lymphadenopathy. A grade II systolic murmur was audible at the apex. The lower border of his liver was palpable 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 5.7×10^9 /l, leukocyte differential count: segmented neutrophils 48%, lymphocytes 42%, monocytes 6%, eosinophils 4%. Platelets 184×10^9 /l. Reticulocyte count was 10.5%. Urine analysis: protein trace, urobilinogen (+), urine bilirubin (-). Icteric index (II) was 18 units. Serum AST was normal. The serum total bilirubin was 29.07 $\mu\text{mol/l}$. 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 anisocytoses 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 1). In the presence of Ka Huang Min solution, the patient serum contained an antibody that agglutinated with untreated "O" red cells with or without complement. The serum was also reactive with paracetamol-coated "O" red cells at 37°C. The results implicated that paracetamol-dependent hemolysis was via both immune complex and drug adsorption. If there were autoantibodies (DAT titer 1:4), which remained testable. In December, 1985, Hb reached to 92g/l, and reticulocyte count was declined to 2.6%.

Test reagent mixture	IAT
Patient's serum + O red cells coated with Ka Huang Min solution*	+
Patient's serum + O red cells coated with caffeine	-
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	-

Table 1: Reactivity of patient' serum with normal untreated "O" RBCs in various reagent conditions.

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

Case 2: On September 4, 1985, a 34-year-old man was admitted to hospital 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 3000 ml traditional decoction. Traditional medicine included *Kudzuvine* root (radix Pueraria), *Serissa japonica* (*Serissa serissoides*) and *Origanum vulgare* (wild mint). 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°C. 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°C, 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 splenomegaly. Laboratory

evaluation: Hb 51 g/l, WBC 14.7 x 10⁹/l, leukocyte differential count: segmented neutrophils 81%, lymphocytes 16%, monocytes 2%, eosinophils 1%. Platelets 208 x 10⁹/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. AST and ALT were normal results. van den Bergh was indirect positive. Rous test, Ham test (the acid-serum lysis test), heat lysis test, sucrose hemolysis test, Isopropanol test and cold agglutinin test were all 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 anisocytoses and poikilocytosis. Electrophoresis of serum and hemoglobin electrophoresis were normal results.

Test reagent mixture	IAT	
	Agglutination	Hemolysis
Patient's serum + drugs* + O RBCs	-	-
Patient's serum + drugs* + complement** + O RBCs	-	-
Patient's serum + <i>Kudzu</i> vine root- coated RBCs	-	-
Patient's serum + <i>Origanum vulgare</i> - coated RBCs	+ (titer 1:4)	+
Patient's serum + <i>Serissa serissoides</i> -coated RBCs	-	-
Normal serum + <i>Origanum vulgare</i> - coated RBCs	-	-

Table 2: Reactivity of patient's serum with normal untreated or papain- treated O RBC's in various reagent conditions. 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

To confirm the drug-induced immune hemolytic anemia (DIIHA), the drug-related serological tests performed according to standard methods (Table 2). The titer of drug antibody was 1:4. The experimental results indicated the diagnosis of herbs wild mint induced DIIHA, which was mediated by drug-adsorption mechanisms. 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 6.5 x 10⁹/l, platelets 109 x 10⁹/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.

Case 3: On February 4, 1990, a 16-year-old boy was the chief complaint of a sudden drops of blood from nostril, and intermittent up to about 5 hours. On February 15,1990, an episode of repeat epistaxis 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 10⁹/l, leukocyte differentiate count: 26 - 33% segmented neutrophils, 67 - 74% lymphocytes. Platelets count was 30 x 10⁹/l. Bone marrow was the definite diagnosis of aplastic anemia on March 6, 1990. There was no useful following various combination regimen of conventional western and traditional medicine. At that time, the patient occasionally passed out, and he caught a persistent fever over 39°C. After grinding and drink with rhinoceros horn solution daily, the processed plan was considered the combination of methyltestosterone (30 mg/day), leucogen, vitamin B4 (adenine) and Batilol and levamisole. Remission was obtained following 4 months treatment duration. An induction of breast tumours was unexpectedly uncovered by the use of 6+ months of methyltestosterone treatment, and tumour was progressive regressed after stopping this drug for four months. The patient had a health child. He is a well survivor now.

Case 4: On August 21, 1996, a 34-year-old woman was admitted to the hospital due to her nephrotic syndrome and renal insufficiency for 3 years. On admission, she was chief complaint of severe pallor, fatigue and facial edema. At physical examination, she had a percussion of bilateral flank pain. Ascites +++. BP 120/80 mmHg. Urine analysis: protein 4+; sediment: 1 - 2 RBC/HP and 4 - 6 WBC/HP. Blood chemistry showed BUN 7.7 mmol/l (control: 2.9 - 7.1 mmol/l). She was given penicillin G sodium and dexamethasone intravenously, with traditional medicine and adjuvant intramuscular testosterone. The drugs vitamin C and Ferrous sulfate tablets were also given orally. On August 29, 1996, proteinuria was declined to 1+. The traditional medicine and testosterone were continued to be taken later. On September 8 and October 24, 1996 respectively, repeat urinalysis showed protein negative. Traditional medicine consisted of *Codonopsis pilosula*, *Astragalus membranaceus* (30 - 60g), *Radices rehmanniae*, *Angelica sinensis*, *Ophiopogon japonicus*, daizheshi (processed Haematite), *Lycium barbarum* (wolfberry), *poria cocos*, *polyporus umbellata*, *Rhizoma anemarrhenae*, orange peel. She died of severe renal failure, and she was 8 years survivor.

Case 5: On May 3, 2000, a 19-year-old man was admitted to hospital because of dizziness and progressive fatigue for more than half a year, and a recent episode of epistaxis for 10 days. Physical data on admission disclosed anemia. The temperature was 38.5°C. Ear, throat and ocular examination were normal. There was no obvious abnormality as to heart and both lungs. His heart rate was 105 beats per minute. There was no lymphadenopathy, hepatomegaly, or splenomegaly. He had a past history of hepatitis B. Laboratory data: on admission, blood findings were Hb 90 g/l, decreased WBC, platelets $20 \times 10^9/l$. Bone marrow showed a marked hypoplasia. Bone marrow differential count: 29.6% myeloid, of them band and segmented neutrophils accounting for 27.7%, 5.5% orthochromatic normoblasts, 38.8% lymphocytes, and 7.4% plasmacytes. An almost complete marrow depression was apparent. The diagnosis of aplastic anemia was made. Treatments consisted of a combination regimen of methyltestosterone, stanozolol, levamisole and prednisone tablets, and adjuvant with traditional medicine. An additional use included intravenous phytohaemagglutinin for 1 week in order to accelerating the number recovery of CFU-S and initiating DNA synthesis of cells. After 4 months of oral methyltestosterone, he was forced to discontinuing this drug due to his breast swelling and pain and suspected breast tumour. The patient was once receiving subcutaneous erythropoietin. On October 26, 2000, complete remission in peripheral blood was obtained following the combination treatment for near 6 months. Because of without undergoing continuous treatment, on April 2002, the patient was transferred to another hematological hospital following the recurrence of aplastic anemia. He is a survivor now.

Case 6: On October 16, 2003, a 31-year-old man was the chief complaint of his pallor and fever for 15 days. On admission, physical examination showed a marked anemia and hepatomegaly. Persistent fever reached to 39°C. Chest X-ray showed small amount of hydrothorax. Liver CT scan demonstrated a $7.0 \times 4.5 \text{ cm}^2$ mass which was considered as secondary hepatic tumor. AFP was negative. Laboratory data: hemoglobin concentration (Hb) was 53 g/l, white blood cells (WBC) count was $3.4 \times 10^9/l$, leukocyte differential count in blood smear: 20% promyelocytes. The platelet count was $2.4 \times 10^9/l$. Bone marrow aspiration revealed normal cellularity. Bone marrow differential count showed 77% promyelocytes. The patient was diagnosed as acute promyelocytic leukemia (APL) complicated with secondary hepatoma. Treatment consisted of 80 mg/day of retinoic acid (RA) and 1 mg/day of homoharringtonine 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 blasts and promyelocytes. On the routine peripheral blood smear uncovered no immature myeloid cells. Hemogram: Hb 102 - 108 g/l, WBC $7.7 - 5.0 \times 10^9/l$, platelets $229 \times 10^9/l$. CR was obtained after 1-month period of RA, chemotherapy and traditional medicine. He died of APL relapse (94% blasts and promyelocytes in peripheral blood and in bone marrow) 20 months later. The repeated liver scan found the complete regression of his liver tumor albeit the recurrence of his leukemia.

Case 7: 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 $1.90 \times 10^{12}/l$ (control: $4.0 - 5.5 \times 10^{12}/l$), WBC $2.6 \times 10^9/l$, platelet count $11.8 \times 10^9/l$. 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. On the peripheral blood smear, the erythrocytes showed anisocytosis and poikilocytosis, and there was occasional normoblast per 100 leukocytes. The characteristic hypersegmented neutrophil of the peripheral blood are relatively found. The patient had a past history of gastritis. The diagnosis of refractory anemia or pernicious anemia was made. Treatment consisted of a regimen of full doses of hematopoietic stimulating agents vitamin B12 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* (wolfberry), semen coiois, stiff silkworm, daizheshi (processed Haematite), *Ophiopogon japonicus*, donkey-hide gelatin, poria cocos, orange peel, licorice (glycyrrhiza). 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 30.3 pg (27.8 - 33.8 pg), MCHC 265 g/l (320 - 355 g/l), RBC $2.19 \times 10^{12}/l$ ($4.09 - 5.74 \times 10^{12}/l$), WBC $2.3 \times 10^9/l$ ($4 - 10 \times 10^9/l$), platelet $152 \times 10^9/l$ ($100-300 \times 10^9/l$). Faeces for occult blood test (OBT) was weak positive. CR was obtained by the use of traditional medicine and erythropoiesis-stimulating agents vitamin B12 and folate growth factor. During the follow up of 9 years, he remained well now.

Discussion

In this study, a series of the long follow up of 30 different types of anemias were reported. Until now, as to DIIHA, about 130 drugs has been incriminated. Regarding 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. Drug-dependent antibody formation is most commonly caused by penicillin, piperacillin, along with cefotetan and ceftriaxone [1-6]. We reported 2 patients with penicillin- induced DIIHA previously (Lin Zhusan., *et al.* 1984, data not shown). Two additional paracetamol -dependent and herbs wild mint- induced DIIHA were presented here.

As a novel retinoic acid (RA) to APL treatment, this specific APL harboring oncogenic pml/RARa fusion. 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 or UPS proteosome system, immature promyelocytes toward maturation. Finally, APL patients obtained complete remission (CR) (see the following figure, George Zhu, 1990-91) [9-15]. Therefore, we cannot say that the drug retinoic acids stimulate (bind to) a pml/RARa oncogene. This model is first described in eukaryotes.

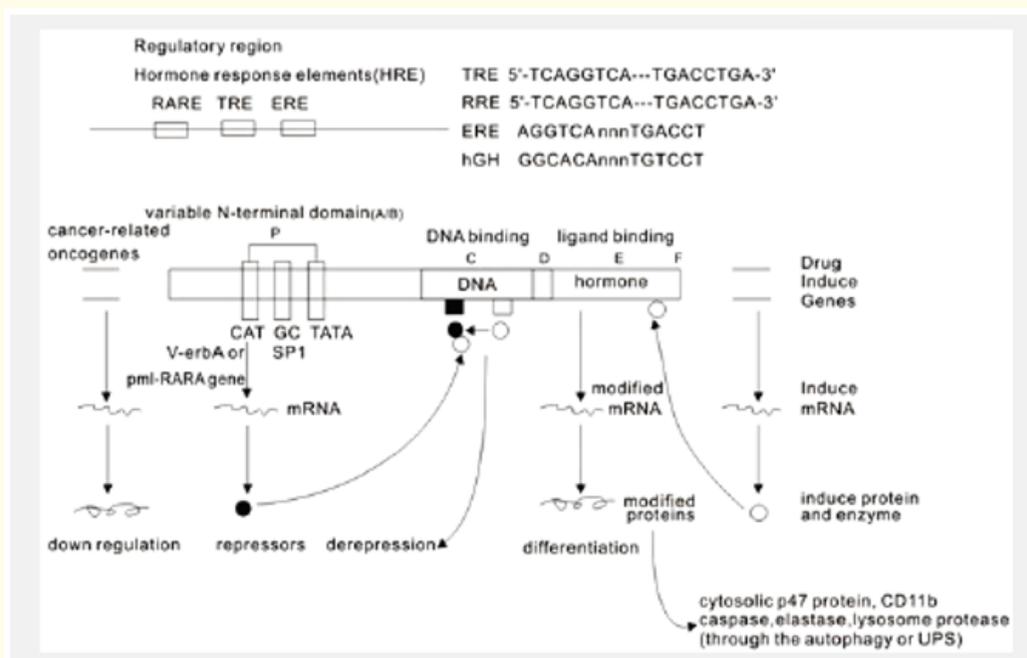


Figure 1: Molecular model of the gene regulation of retinoic acid (RA) action.

Conclusion

Anemia is a low number of red blood cells. Women during pregnancy, young children and long-term diseases were predispose to anemia. Anemia could be categorized into three types: blood loss (e.g. gastrointestinal ulcer or cancer), decreased or faulty red cell production (e.g. stem cell problems, or iron, vitamin B12 and folate deficiency), and by destruction of red blood cells such as drug-induced immune hemolytic anemia (DIIHA). Based on these intention, an attempt design is place in proper analytic approach to review 30 patients with anemia in this study. Apparently, iron deficiency anemia or megaloblastic anemia could be cured following the prescribed supplement of iron or vitamin B12 and folate. With marrow transplantation [8], the majority of aplastic anemia established long-term hematopoiesis and returned to a fully functional life. Steroid hormone (e.g. prednisone) and traditional medicine were occasionally promising benefits in nephrotic syndrome and renal insufficiency. For immune hemolysis, see a comprehensive work and review by Petz and Garratty [2]. In conclusion, early interceptive treatment of anemia and achieving long-term complete remission in malignant tumours is still major challenge in future.

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