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CLINICAL EFFECTIVENESS OF TRANSFUSION OF A DRY LEUCOCYTIC MASS IN LEUCOPENIC CONDITIONS

/Following is a translation of an article by graduate student M.E. Mirzoyeva in Azerbaydzhanskiy Meditsinskiy Zhurnal (Azerbaydzhan Medical Journal), Vol XXXIX, No 11, Baku, 1962, pages 15-20./

Azerbaydzhan Scientific Research Institute of Hematology and Blood Transfusion (Director -- Docent G.A. Guseynov, , Scientific director -- Corresponding Member of the Acad Sci AzSSR, Prof F.A. Efendiyev)

In recent years various blood preparations of directed action have found wide clinical use, such as the thrombocytic mass in Werlhof's disease and the leucocytic mass in leukopenic conditions (A.A. Bagdasarov and associates, G. Abdullayev).

In 1956 we conducted a complex work at the Azerbaydzhan Scientific Research Institute of Hematology and Blood Transfusion on obtaining and studying the clinical effectiveness of a native leucocytic mass (Prof F.A. Efendiyev, candidate of medical sciences A.M. Akhundova, candidate of medical sciences T.Ya. Goncharskaya, M.E. Mirzoyeva, Sh.M. Beybutov, and O.Kh. Ter-Mkrtycheva). The obtained data showed that, despite a massive radiation effect which resulted in leukopenia in almost every case, thanks to the administration of the leucocytic mass not only was a stabilization of the number of leucocytes observed but also the tendency toward a certain increase in the latter.

Comparative experiments conducted showed that in morphological and functional indexes the leucocytes composed of leucocytic masses prepared according to the method of the Central Order of Lenin Institute of Blood Transfusion (TsOLIPK) from cation blood and to the Azerbaydzhan Institute of Blood Transfusion (AzIPK) method from citrate of magnesium blood, are analogous. At the same time, the leucocyte indexes from leucocytic mass prepared from blood which had been

stabilized by heparin and from blood prepared on a citrate solution according to the TsOLiPK prescription No 7, are lower than the first indexes.

The use of leucocytic mass prepared by the AzIPK method in the clinic showed that the leucocytic mass constitutes an effective means of treatment of leukopenia of radiation origin, hypoplastic anemias, and agranulocytoses.

We also recommended transfusion of the leucocytic mass for prophylactic purposes to patients who had been subjected to radiation therapy.

Despite the fact that our leucocytic mass is a sufficiently effective preparation in the treatment of various leukopenic states, there is nevertheless a serious drawback in that it is impossible to store it for more than 24 hours. Starting on the 2nd-3rd day, a destruction of leucocytes is observed. It was noted that a leucocytic mass which had been preserved for several days (four to six days) despite the fact that most of the leucocytes in it were in the state of destruction, proved to be effective in regard to the increase of the leucocyte content upon transfusion, almost to the same extent as the transfusion of a freshly-prepared leucocytic mass.

In working with the native leucocytic mass, we conceived the idea that not only the viable leucocytes, isolated from donor's blood can stimulate leucopoiesis, but also the component part -- protoplasm and nucleus -- as well as the biological products of disintegration of leucocytes -- the nucleic acids -- may possess the irritating and stimulating effect on the leucopoietic system. In addition, the products which are formed upon drying of the leucocytes and their subsequent dissolution and transfusion may, upon their subsequent splitting within the organism, serve as a sort of plastic material for the formation of compounds which enter into the composition of new leucocytes of the recipient. On basis of this Prof F.A. Efendiyev suggested in the preservation of leucocytes that new ways be tested, namely, their storage in a dried state, and that the clinical effectiveness of such preparations in the leukopenic state be studied.

For experimental purposes the blood for drying the leucocytic mass was prepared on a preserving solution, as per the prescription of Prof Efendiyev, and from preserved citrate blood according to prescription 7 "b".

Generally about 40.0 ml of native leucocytic mass is obtained from 450.0 ml of preserved blood. Drying was carried out by the method suggested by TsOLiPK (by T.Ya. Rozenberg) for drying the plasma under vacuum conditions at 40-50° temperature. Drying of the leucocytic mass was carried out

in flasks, placed in a water bath and heated to 40-50°; the leucocytic mass is poured into a flask by the drip method. The falsk in which the drying takes place is connected with a moisture condenser which is placed in a cooling ice bath. The apparatus is connected with vacuum-pump through the cotton filter of the condenser. Prior to drying, to each 40.0 ml of leucocytic mass 10 to 15 cm^3 are added of a 40 percent solution of glucose, so as to obtain complete solubility of the dried preparation when it is being transfused.

The advantage of this method consists of obtaining a complete reversible solubility of the dried preparations; the rate of drying is three to four hours.

The dry leucocytic mass passed bacteriological control according to the standard system for dry plasma. The dry leucocytic mass was sterile in every case.

In order to ascertain the possibility of toxicity of the solution, tests were carried out on white mice. Each production series was checked also for the presence of pyrogenic substances in the solution of the dry leucocytic mass on healthy rabbits, according to generally accepted methods of intravenous administration of the solution and a preliminary and subsequent measuring of rectal temperature.

For the study of the anaphylactogenic properties of the solution of the dry leucocytic mass, experiments were conducted on guinea pigs and rabbits, as per the A.M. Bezrodko method (1928).

Thus, the investigations conducted enabled us to develop a more precise method of drying the leucocytic mass, to evaluate experimentally the biological effect of a dried and dissolved leucocytic mass, as well as the tolerance by animals of an intravenous injection of a solution of dry leucocytic mass, and to arrive at the following conclusions.

1. Solutions of a dry leucocytic mass, dried in a vacuum-apparatus at a positive temperature of 40-50°, do not possess any toxic properties upon transfusion under experimental conditions.

2. Upon checking the solutions of the dry leucocytic mass for the presence of pyrogenic substances, the findings proved to be negative in every case.

3. Solutions of the dry leucocytic mass possess no anaphylactogenic properties.

4. These data permit the assumption that dry solutions of a leucocytic mass are well tolerated by the recipient. The experimentally obtained positive results enabled us to employ the dry leucocytic mass, prepared according to the above-described method from the donor's blood, in the clinic for the treatment of patients suffering from leukopenia of various etiology.

The leucocytic mass was administered in the amount of 40.0 ml, diluted in twice-distilled water, intravenously as well as intramuscularly. A total of 122 intravenous and 64 intramuscular infusions were performed.

A total of 28 petients received the dry leucocytic mass.

Each patient received an average of five to 10 infusions. According to the diagnosis, the patients were divided as follows: metamalarial splenomegalia with phenomena of hypersplenism -- six, agranulocytosis -- three, iron-deficiency anemia of gastrogenic etiology with leukopenia -- five, leukopenia after radiation therapy for cancer of the internal organs -- nine, leukopenia which had originated following administration of thio-tepa in oncological patients -- five.

Of 28 petients, 18 were treated in the clinical department of the AzIPK and 10 in the clinical department of the Institute of Roentgenology and Radiology.

Six individuals aged 26 to 57 years were suffering from metamalarial splenomegaly with phenomena of hypersplenism.

Hemoglobin ranged between 14 percent and 75 percent, erythrocytes -- from 1,000,000 to 4,360,000, reticulocytes from 2 percent to 9 percent, thrombocytes from one to 161,000, leucocytes from 1100 to 8400, eosinophiles from 1 percent to 13 percent, rod-nuclear from 2 percent to 15 percent, segmentonuclear from 40 percent to 64 percent, lymphocytes from 11 percent to 41 percent, monocytes from 2 percent to 9 percent.

The spleen protruded from the hypochondrium two to six cm, and the liver -- one to four cm.

Apparently, in patients suffering from metamalarial aplenomegalia, together with leukopenia, there was also anemia and thrombocytopenia present. Therefore, in a number of cases (in three patients), simultaneously with the infusion of a solution of dry leucocytic mass at 40.0 ml every other day intravenously or intramuscularly, the patients also received Vitamin B_{12} and iron preparations.

After a course of treatment which comprised five to 10 infusions of a solution of dry leucocytary mass combined with preparations of iron and Vitamin B_{12}, a considerable increase was noted in the indexes of red blood, as well as of leucocytes and thrombocytes.

Hemoglobin varied from 53 percent to 83 percent, erythrocytes from 2,980,000 to 4,670,000, reticulocytes -- 2 percent to 32 percent, thrombocytes -- 34 percent to 69 percent, leucocytes -- 3200 to 10500, eosinophiles -- 2 percent to 4 percent, rod-nuclear -- 2 percent to 12 percent, segmentonuclear -- 58 percent to 65 percent, lymphocytes -- 20 percent to 32 percent, monocytes -- 6 percent to 11 percent.

Upon comparing it with the group of patients suffering from splenomegaly who had received no dry leucocytic mass but a transfusion of whole blood, no particular difference was observed. Although the number of leucocytes rose above the initial figure, it nevertheless was of a transitory nature.

Three agranulocytosis patients (two 48 years old and one -- 61 years) were admitted to the clinic in a serious condition.

For example, the Hb comprised 53 percent to 73 percent, erythrocytes -- 3,000,000 to 3,920,000, reticulocytes -- 12 percent to 17 percent, thrombocytes -- 60 percent to 62 percent, leucocytes -- 400 to 1400, eosinophiles -- 0 percent to 1 percent, rod-nuclear -- 2 percent to 12 percent, segmentonuclear -- 23 percent to 46 percent, lymphocytes -- 2 percent to 98 percnet, monocytes -- 2 percent to 6 percent.

In two cases an infusion of the solution of the dry leucocytic mass combined with Vitamin B_{12} and sodium nucleinate considerably improved the patient's condition and contributed to the normalization of the peripheral blood. In the third case the complex therapy employed proved to be ineffective, the patient's condition took a turn for the worse, and the patient (female) died.

An improvement was noted in two patients after a course of complex treatment:

In these patients the hemoglobin was varied from 64 percent to 87 percent, erythrocytes -- from 3,920,000 to 3,940,000, reticulocytes -- 12 percent to 17 percent, thrombocytes -- 60 percent to 62 percent, leucocytes -- 3300 to 4000, eosinphiles -- 0, rod-nuclear -- 2 percent to 12 percent, segmentonuclear -- 15 percent to 61 percent, lymphocytes -- 30 percent to 80 percent, monocytes -- 3 percent to 13 percent.

Five patients, aged 27 to 43 years were suffering from iron-deficiency anemia of gastrogenic etiology and leukopenia.

In this group Hb varied from 30 percent to 48 percent, erythrocytes -- 2,600,000 to 3,820,000, reticulocytes -- 6 percent to 18 percent, thrombocytes -- from 10 percent to 45 percent, leucocytes -- 2000 to 3300, eosinophiles -- 1 percent to 4 percent, rod-nuclear -- 1 percent to 8 percent, segmentonuclear -- 51 percent to 66 percent, lymphocytes -- 25 percent to 36 percent, monocytes -- 2 percent to 14 percent.

Following a course of treatment (infusion of a solution of the dry leucocytic mass five to 10 times, at 40.0 ml, combined with iron preparations, steroid hormones, and injections of Vitamin B_{12}) an improvement in the condition of the patients was noted.

For instance, in the blood an appreciable increase was

observed in the amount of erythrocytes and leucocytes; however, it did not reach norm in every case. Hb varied from 40 percent to 64 percent, erythrocytes -- 3,610,000 to 4,070,000, reticulocytes -- 14 percent to 19 percent, thrombocytes -- 30 percent to 43 percent, leucocytes -- 3700 to 6300, eosinophiles -- 1 percent to 7 percent, rod-nuclear -- 2 percent to 8 percent, segmentonuclear -- 45 percent to 60 percent, lymphocytes -- 31 percent to 34 percent, monocytes -- 2 percent to 10 percent.

We had under observation nine patients with leukopenia of radiation origin who had received the dry leucocytic mass at the therapeutic department of the Institute of Roentgenology and Radiology. Six of them were females and three, males. Their age varied between 30 and 65 years.

As to diagnosis, the patients were divided as follows: blastoma of the esophagus -- four, melanoma of the right heel region -- one, blastoma of the left lung -- one, cancer of the uterine cervix -- three.

Every patient received combined radiation therapy (roentgenotherapy and telegammatherapy with radioactive cobalt) and a transfusion of a dry leucocytic mass. The control patients (10 individuals) received only a combined radiation therapy without the transfusion of a dry leucocytic mass.

The conditions of therapy, amount of dose, method of radiation, and periods of application of the therapeutic dose to the tumor focus were identical in both groups.

Patients with the diagnosis of cancer of the uterine cervix (three individuals) received X-ray therapy from four-six fields by means of a total skin dose of 10,000 to 16,000r on a RUM apparatus under conditions of deep X-ray therapy and application of radioactive cobalt to the cervix, fornices, and uterine cavity in doses of 2,500 to 7,000 r. The radiation periods were within the limits of four to eight weeks. Four patients were subjected to telegammatherapy on a GUT-Co-400 device for a blastoma of the esophagus, one -- for the blastoma of the left lung, and one -- melanoma of right heel region, in the total dose of 8,000 to 12,800 r.

In these patients Hb varied from 62 percent to 82 percent, erythrocytes -- 3,840,000 to 5,100,000, thrombocytes -- 113,210 to 311,100, leucocytes -- 1400 to 5700, eosinophiles -- 1 percent to 14 percent, rod-nuclear -- 1 percent to 13 percent, segmentonuclear -- 47 percent to 70 percent, lymphocytes -- 14 percent to 39 percent, monocytes -- 2 percent to 8 percent.

Following treatment the blood picture was as follows: Hb -- 60 percent to 80 percent, erythrocytes -- 3,910,000 to 5,370,000, thrombocytes -- 127,800 to 311,000, leucocytes --

3100 to 8400, eosinophiles -- 1 percent to 6 percent, rod-nuclear -- 5 percent to 11 percent, segmentonuclear -- 52 percent to 70 percent, lymphocytes -- 12 percent to 37 percent, monocytes -- 3 percent to 6 percent.

Thus, upon the combination of injection of a dry leucocytic /mass/ solution /and radiation therapy/ the effectiveness of the leucocytic mass /proved to be greater/, especially in cases where the leucocytic mass was employed for prophylactic purposes, in order to prevent the development of leukopenia in oncological patients who were receiving radiation therapy.

Of interest and meriting attention are our data which show the considerable therapeutic effect from the administration of a solution of dry leucocytic mass to patients with various malignant tumors who have been receiving a strong cytostatic substance such as thio-tepa.

Under our observation were five patients who received simultaneously with thio-tepa the leucocytic mass intramuscularly at 40,0 ml daily during the entire period of thio-tepa administration.

In these patients, prior to treatment, the amount of Hb was varied from 66 percent to 80 percent, erythrocytes -- 3,380,000 to 4,670,000, reticulocytes -- 2 percent to 19 percent. thrombocytes -- 37 percent to 52 percent, leucocytes -- 2600 to 6000, eosinophiles -- 1 percent to 3 percent, rod-nuclear -- 4 percent to 7 percent, segmentonuclear -- 59 percent to 81 percent, lymphocytes -- 8 percent to 24 percent, monocytes -- 2 percent to 9 percent.

Following the course of thio-tepa therapy (200-300 mg combined with injections of a solution of dry leucocytic mass) the amount of Hb varied from 61 percent to 80 percent, erythrocytes -- 3,590,000 to 4,670,000, reticulocytes -- 8 percent to 14 percent, thrombocytes -- 45 percent to 52 percent, leucocytes -- 4300 to 6400, eosinophiles -- 2 percent to 10 percent, rod-nuclear -- 2 percent to 10 percent, segmentonuclear -- 60 percent to 73 percent, lymphocytes -- 11 percent to 27 percent, monocytes -- 4 percent to 15 percent.

Thus, upon combining injections of a solution of the dry leucocytic mass with th' o-tepa, the amount of leucocytes did not decrease below normal figures, whereas in patients of the control group who have been receiving only thio-tepa and even in combination with pentoxyl or tesan, the amount of leucocytes is reduced to critical levels at the end of the course of therapy, and in a number of cases it is necessary to discontinue the administration of the preparation.

Conclusions

1. The dry leucocytic mass can be recommended for use in combination with other therapeutic preparations (Vitamin B_{12}, steroid hormones) in the treatment of patients suffering from agranulocytosis.

2. In leukopenia of radiation etiology, especially when the dry leucocytic mass had been employed simultaneously with radiation therapy in the prevention of the radiation syndrome, the dry leucocytic mass proved to be more effective than the available medicinal preparations: tesan, pentoxyl, sodium nucleinate, and leucogen.

3. Transfusion of the dry leucocytic mass to patients receiving thio-tepa therapy creates the possibility of a prolonged use of thio-tepa without the onset of the leukopenic syndrome.

4. Our clinical use of the solution of dry leucocytic mass demonstrated that it is of little effect in its transfusion to patients suffering from metamalarial splenomegaly and leukopenia.

5. The convenience of its storage and the satisfactory effectiveness of the dry leucocytic mass, especially in patients receiving radiation therapy enabled us to recommend the manufacture of dry leucocytic mass with the view of introducing it into the practice of therapeutic institutions.

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