Spontaneous Hematologic Recovery From Bone Marrow Aplasia After Accidental Tenfold Overdosage With Radiophosphorus


Two patients with polycythemia vera received intravenously an accidental tenfold overdosage of radiophosphorus therapy (60 and 50 mCi 32P, respectively). In both patients, the occurrence of hemorrhagic complications 3 wk after the 32P medication led to detection of the error and referral to our hospital. Upon admission they showed an agranulocytosis, severe thrombocytopenia, and bone marrow aplasia. In both cases, spontaneous recovery of the hematopoiesis was observed from day 40 posttreatment onward. In one patient, a slow but ultimately complete normalization of blood counts and marrow morphology took place, whereas in the other, a mild thromboctopenia persists. Nearly 5 yr after the accidental overdosage, both patients are clinically well. Symptoms of polycythemia vera have not reappeared up to now. Attempts were made to evaluate the radiation dose absorbed by the bone marrow. In the first patient, the daily 32P excretion was determined from day 22 to day 60, whereas in the other patient a whole body count was performed on day 78 after administration. From these results, an approximate cumulative bone marrow dose of 10 Sv (1000 rem) could be calculated.

The hematologic manifestations of whole body irradiation have been extensively studied.1 From these investigations it can be concluded that the bone marrow is one of the most radiosensitive organs of the body. Accidental overdosage followed by bone marrow aplasia is a potential hazard of the therapeutic use of radioisotopes. Due to the care with which isotopes are handled, actual overdosage has rarely occurred.2,3 We are reporting two patients with polycythemia vera, who received an accidental tenfold overdosage of intravenously administered radiophosphorus (32P). The error was due to an incorrect volume dilution of 32P activity by the supplier, which was recognized on day 20 after administration.

Materials and Methods

Case Report: Patient L.M.

This 78-yr-old housewife was in good health until September 1977, when a routine control revealed an elevated red cell count. On clinical examination, no hepatosplenomegaly or lymphadenopathy were detected. Body weight was 59 kg, body height 160 cm. Routine blood chemistry, urine analysis, chest x-ray, arterial blood gases, and lung function tests were all normal. Hematologic values are shown on Table I. The slightly hypercellular bone marrow showed increased erythropoiesis, abundant megakaryocytes, and normal myelopoiesis. The diagnosis of polycythemia vera was made at an outpatient hospital on the basis of repeatedly elevated hemoglobin, red cell and hematocrit values, and no positive clinical and laboratory findings for secondary erythrocytosis. It was therefore decided to administer 32P. On September 22, 1977 (designated as day 0), the patient received 60 mCi 32P intravenously instead of the intended 6 mCi. By day 15 she reported a red-colored urine. On day 22, a severe leuko- and thrombocytopenia was detected and the patient was referred to the University Hospital of Zurich.

On admission, the patient was afebrile and in fairly good condition. Besides multiple petechiae, the clinical examination was normal. Peripheral blood counts were: hemoglobin 15.4 g/dl, reticulocytes 3000 cu mm, hematocrit 41.5%, erythrocytes 5.22 x 106 cu mm, leukocytes 1300 cu mm (granulocytes 71%, monocytes 4%, lymphocytes 25%), thrombocytes 4500 cu mm. The bone marrow was severely hypoplastic. The subsequent blood counts are shown in Fig. 1. The patient was kept in strict reverse isolation, received sterile food and poorly absorbable oral antibiotics (Gentamycin, Vancomycin, Mycostatin) for gastrointestinal decontamination from day 23 to day 49. HLA-A, B-identical single donor platelet transfusions were indicated three times, but otherwise no transfusions were needed. The clinical course was uneventful. The bone marrow aspirate on day 41—although still hypocellular—was repopulated by some islands of active hematopoiesis, and soon afterwards, the peripheral blood counts began to rise. The patient was discharged in good clinical condition on day 59. She returned to normal active life, underwent complete hematologic remission, and has now been well for nearly 5 yr.

Case Report: Patient R.E.

This 73-yr-old housewife underwent a left-sided mastectomy and local irradiation because of breast cancer in 1972. A polycythemia vera had been suspected since 1970, but specific therapy was withheld until 1977, when bone pain, pruritus, and abdominal discomfort occurred. Clinical examination revealed a splenomegaly (13 cm below the left costal margin), acrocyanosis, and cardiac insufficiency. Body weight was 45 kg, body height 153 cm. Peripheral blood counts, bone marrow morphology, blood and red cell volume were consistent with polycythemia vera (Table 1). No metastases of the breast cancer were detected by clinical and laboratory investigations, including x-ray and technetium scintigraphy of the skeleton. Following withdrawal of 400 ml of blood, the patient received intravenously 50 mCi 32P (instead of the intended 5 mCi) on September 21, 1977 (day 0). Two weeks later, she observed multiple petechiae and gingival bleeding. Following extraction of three teeth, an uncontrollable hemorrhage occurred, and the patient was referred to the University Hospital of Berne on day 20.

On admission, the patient was in poor clinical condition. The body temperature was 38.2°C. Oozing from her gingival wounds and
multiple petechiae were observed. The spleen was palpable 3 cm below the left costal margin (in contrast to 13 cm before $^{32}$P administration). The peripheral blood counts were: hemoglobin 13.3 g/dl, reticulocytes 4000 cu mm, erythrocytes $3.55 \times 10^6$ cu mm, leukocytes 700 cu mm (50% granulocytes, 2% basophils, 2% eosinophils, 6% monocytes, 40% lymphocytes), thrombocytes 1000 cu mm. The bone marrow smear and biopsy showed a nearly complete aplasia with a few erythroblasts and myelocytes. Megakaryocytes were absent. During the next days, the blood counts continuously decreased (Fig. 1). The patient was given parenteral antibiotics (Gentamycin, Carbenicillin) and kept in strict reverse isolation. A total of 15 red cell and 31 platelet concentrates were transfused over the next 3 wk. The clinical course was complicated by a necrotizing infection on the lips. By day 43, the leukocyte and platelet count

| Table 1. Laboratory Findings in Patients L.M. and R.E. Prior to $^{32}$P Administration |
|---------------------------------|----------------|----------------|
|                                  | Patient L.M.   | Patient R.E.   | Normal       |
| Arterial blood gas analysis     |                |                |
| O$_2$ saturation (%)            | 97             | ND             | 95–98        |
| pao$_2$ (mm Hg)                 | 86             | 81–99          |
| paco$_2$ (mm Hg)                | 26             | 36–40          |
| Blood volumes                   |                |                |
| Red cell volume (ml/kg)         | ND             | 66.8           | <25          |
| Plasma volume (ml/kg)           |                | 66.2           | <39          |
| Peripheral blood counts         |                |                |
| Hemoglobin (g/dl)               | 18.4           | 18.5           | 12.3–15.8    |
| Hematokrit (%)                  | 56             | 55             | 37–47        |
| Erythrocytes (10$^6$/cu mm)     | 6.85           | 7.11           | 4.0–5.2      |
| Leukocytes (10$^3$/cu mm)       | 8.5            | 30.0           | 3.7–9.6      |
| Platelets (10$^3$/cu mm)        | 190            | 180            | 150–350      |
| Alkaline leukocyte phosphatase  | 252            | 260            | 31–46        |
| Uric acid (mg/dl)               | ND             | 9.5            | <6           |

ND = not determined

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began to rise and a bone marrow biopsy showed foci of active hematopoiesis. Subsequently, the infection cleared and the patient was discharged on day 51 in fairly good clinical condition. The previously enlarged spleen was no longer palpable. The patient underwent nearly complete hematologic remission and has now been well for nearly 5 yr.

**Hematologic Methods**

Serial complete blood counts were performed by routine laboratory methods (Coulter Counter S and Thrombo Autocounter Technicon). Platelet counts below 50,000 cu mm were determined by manual phase contrast microscopy counting according to Feissly and Lüdin.4 Bone marrow smears and biopsies were obtained from the iliac crests by use of the Yamshidi needle and stained by routine methods. At least 300 bone marrow cells per specimen were differentiated.

**Whole Body Counting**

Assessment of 32P total body activity of patient R.E. at day 78 was made in a liquid whole body counter (WBC Packard Instruments). The bremsstrahlung (radioactive counts) emitted due to deceleration of beta particles in the tissue were counted in a liquid scintillator of 900 liter of Shellsol A with CIBA BBOT in a hollow cylinder in which the patient was placed. This instrument is of high sensitivity detecting levels as low as 10^-7  μCi whole body activity. The measuring period lasts from 2 to 10 min depending on the activity.

**Excretion Measurements of 32P**

Daily measurements of 32P activities in plasma, red cells, urine, and feces were performed in patient L.M. from day 23 to 60. The activities were determined by measuring the bremsstrahlung intensity within the 1211 energy window. One microCurie 32P standard (Federal Institute for Reactor Research, Würenlingen, Switzerland) were used for calibration.

**Calculation of Absorbed Radiation Dose**

For calculating the radiation dose to the red bone marrow (RBM), the concept of the International Commission on Radiological Protection (ICRP) was used. The dose D(t) to RBM up to time t after administration of 32P is

\[ D(t) = 1.6 \times 10^{-10} \times U(t) \times \text{SEE} \]  

where \( U(t) \) is the number of disintegrations of 32P in the trabecular bone (TB) up to time t after administration, and \( \text{SEE} \) is the specific effective energy, i.e., the energy per gram of tissue imparted to the RBM per disintegration in the TB (MeV/g). Values of SEE are available for the mathematical phantom of the ICRP Reference Man. The value of SEE (RBM ↔ TB) = 2.3 \times 10^{-4} MeV/g (equation 2) given for this phantom was modified according to the actual total body mass of the patient (59 kg) as compared to the mass of the Reference Man phantom (70 kg). For the calculation of this value, 32P is considered as a so-called surface seeker, i.e., due to its short physical half-time, 32P is assumed to be distributed on the bone surface.

The number of disintegrations of 32P in the trabecular bone is calculated by

\[ U(t) = \int_{t'} q(t') \, dt' \]

where \( q(t') \) is the activity in the trabecular bone at time \( t' \). \( U(t) \) is thus determined by the physical half-life of the radionuclide, the biodistribution and retention of phosphorus in the skeleton, which are required for absorbed dose calculations. Since \( U(t) \) or \( q(t') \) are not directly measurable, a function describing the retention of phosphorus in the bone, such as the 4-terms equation given by the ICRP5 can be used. According to this equation, phosphorus entering the transfer compartment is retained there with a half-life of 0.3 days. Of this phosphorus, 15% is assumed to be directly excreted, 15% to go to intracellular fluids, 40% to soft tissue, and 30% to mineral bone where it is assumed to be “permanently” retained. According to the mass ratio of trabecular and cortical bone, 20% of the bone activity \( q(t') \) is estimated to be retained in the former.

For absorbed dose calculation, the applicability of the above model to the present case of L.M. had to be examined. This was achieved by urinary excretion measurements of 32P in this patient.

**RESULTS**

**Peripheral Blood Counts**

The evolution of blood counts following admission on day 22 (case L.M.) and 20 (case R.E.) after the accidental 32P overdosage was very similar in both cases (Fig. 1).

The hemoglobin values were normal on admission in both cases, but declined thereafter. The subsequent evolution may be interpreted correctly in L.M. only, because she received no red cell transfusions and neither bleeding nor infectious complications occurred. In this patient, the hemoglobin level reached the nadir of 7.3 g/dl by day 48. Thereafter, the hemoglobin rose gradually and reached the normal range by day 263. A similar but somewhat slower and less complete recovery of hemoglobin was observed in R.E. following day 44.

The reticulocyte counts were already low on admission in both patients. In L.M., no reticulocytes were found on day 33 and only 3000 cu mm on day 42. Thereafter, the counts rose to high-normal levels from day 49 onward. In R.E., reticulocytes were not determined until day 50, so that the nadir was probably missed.

The leukocyte counts decreased to a nadir of 160 cu mm on day 28 (L.M.) and 130 cu mm on day 23 (R.E.), respectively. The counts remained below 500 cu mm until days 39 and 34, respectively, but thereafter slowly increased and finally normalized by day 84 and 62, respectively.

During the period of severe leukopenia, a nearly complete agranulocytosis (40 cu mm) was documented in L.M., whereas in R.E. no differential white cell counts until day 35 were performed. Subsequently, absolute granulocyte counts rose in both patients reaching values over 500 cu mm on day 49 and 50 and normalizing on day 57 and 62, respectively.

The platelet counts were already very low on admission, and repeated platelet transfusions were needed in both cases. Thrombopoiesis was self-sustained by days 41 and 39. The counts remained over 50,000 cu mm following days 48 and 111. Whereas L.M. normalized

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her platelet count after 1 yr. R.E. showed subnormal values up to the last control after 4.5 yr.

**Bone Marrow**

On admission, the bone marrow smears and biopsies were severely hypocellular in both cases with only a few erythroid and myeloid elements. Megakaryocytes were completely absent. By day 40, the marrow was still hypoplastic, but some islands of active well differentiating hematopoiesis could be observed in both cases. A control biopsy in patient R.E. 1 yr later showed a slightly hypocellular bone marrow, whereby megakaryocytes were most affected. A control biopsy at 2 yr demonstrated a normal bone marrow morphology. In patient L.M., no bone marrow analysis was done after day 40.

**Absorbed Dose Calculation**

In patient R.E., 300 μCi 32P were measured as total body activity on day 78. Assuming a retention function equal to that given by the ICRP concept, this activity corresponds to an initial total incorporated activity of approximately 50 mCi. This value is in good agreement with the dose error reported by the supplier.

The results of the excretion measurements in patient L.M. are shown in Fig. 2. An evaluation of these data shows that the urinary excretion is well described by a single exponential function with a half-life of 21 days ($r^2 = 0.87$). For an administered activity, $q_0$, of 60 mCi, these measured excretion data are in good agreement with the excretion rates calculated using the ICRP model. As there are no data available for the urinary excretion of 32P prior to day 24, this agreement justifies the use of the retention function according to 4-terms equation of the ICRP for calculating $U(t)$ (i.e., the number of disintegrations of 32P in the trabecular bone up to time $t$ after administration). This results for $U(t = \infty)$ in $1.1 \times 10^5 \times q_0$ and for $q_0 = 60$ mCi in $U(t = \infty) = 2.4 \times 10^6$. Using a SEE value adjusted to the body mass of 59 kg [SEE (RBM → TB) = $2.7 \times 10^{-4}$ MeV/g], the radiation dose absorbed in the red bone marrow is 17 rem/mCi administered. For the actually administered activity of 60 mCi, this results in a total radiation dose of 10 Sv (1000 rem). The dose rate decreases according to the physical half-life of 32P. The dose already absorbed at the start of our investigations (day 24) was nearly 80% of the total dose.

**DISCUSSION**

Radioactive phosphorus (32P) has been widely used during the past decades for the treatment of polycythemia vera. It obviously affects the blood by acting on the hematopoietic stem cells of the bone marrow. In the dose range recommended (4-6 mCi), hypoplastic pancytopenia has been an extremely rare complication. At higher dose levels (8-12 mCi), severe bone marrow failure appears to be more common. We are not aware that a single dosage of 32P in the range received by our patients has been administered previously to man intentionally or accidentally. The most severe overdosage was published by Cobau. After an oral dose of 0.4 mCi 32P/kg body weight, his patient suffered from a mild and reversible pancytopenia. The hematologic changes observed in our patients after 1 mCi 32P/kg were much more pronounced. However, a spontaneous recovery of bone marrow function took place in both patients after day 40. A similar interval between 32P administration and beginning marrow recovery was observed in the few cases of pancytopenia following conventional dosage of 32P. As in chronic aplastic anemia, thrombocytopenia was the most refractory aspect of these and our cases. Clinical or hematologic symptoms of the polycythemia vera did not recur in our patients for nearly 5 yr after overdosage. According to the EORTC polycythemia vera study, only 10% of patients treated with 32P remain in remission for such a long period of time.

Attempts were made to estimate the absorbed radiation dose to the red bone marrow. In one patient, urinary excretion of 32P was determined daily and used for the calculation of the radiation dose according to the concept of the ICRP. Since stool specimens were found to contain insignificant amounts of 32P (quantitatively <15% of the urinary excretion for the same day), fecal excretion was not taken into consideration for this calculation. Urinary excretion data of one patient from day 24 to 60 and total body retention of the other patient on day 78 fitted well the ICRP retention function and the erroneous measurement reported by the supplier. Therefore, the ICRP reten-
tion function was used for absorbed dose calculation, resulting in bone marrow doses of approximately 10 Sv (1000 rem) for both patients. On the other hand, it should be mentioned that these dose calculations must be interpreted with caution. Specific information is neither available for excretion data prior to day 24 after $^{32}$P administration nor for the fractional bone retention of phosphorus. The actual retention function of the radionuclide in the skeleton at early times after administration may differ from the function as given in the ICRP model and used here. As a consequence, it is not possible to quantify the range of error of the above dose equivalent value, which should be considered as a best estimate. Others have estimated a higher total dose to trabecular marrow (24 rem/mCi as compared to 17 rem/mCi in our method) using repeated bone marrow biopsy counting.13

Observation of peripheral blood counts are an alternative method enabling assessment of total body radiation dosage. After acute external irradiation, lymphocytopenia occurs in a dose-related and predictable degree.1 Since the overdosage was detected only after 3 wk, lymphocyte counts early after $^{32}$P overdosage are not available for our patients. Regardless of the mode in which the irradiation is received, granulocytopenia and thrombocytopenia develop more slowly. The hematologic changes observed in our patients are consistent with a bone marrow dose of 500–900 rem.1

Because of the likelihood that such an unusually high bone marrow irradiation dose would result in permanent and likely fatal hypoplasia, the gratifying outcome in our patients may be of interest for the management of similar future cases should they ever occur. The survival of both patients is largely due to the management during the prolonged and profound period of hypoplasia consisting in strict reverse isolation, gastrointestinal decontamination, platelet substitution, and antibiotic therapy.

REFERENCES

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Spontaneous hematologic recovery from bone marrow aplasia after accidental tenfold overdosage with radiophosphorus

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