Hematologic Findings in Human Beings Given Therapeutic Doses of Gallium-72

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IN RECENT YEARS there has been an appreciable accumulation of data concerning the hematologic effects of external whole body radiation, but little corresponding data concerning the effects of internally administered isotopes. An opportunity to study these effects occurred when a program entailing the use of gallium$^{72}$ (Ga$^{72}$) in the treatment of patients was undertaken in the Medical Department at the Brookhaven National Laboratory. The therapy was directed at metastatic or diffuse primary bone involvement by malignancy. A similar study was undertaken previously at the Oak Ridge National Laboratories after exhaustive investigation of the chemistry distribution toxicity, etc., of the isotope,$^1$ and clinical findings here were essentially those reported by that group. The present report concerns hematologic observations made on the patients in the course of therapy during their stay in the Brookhaven National Laboratory Research Hospital (BNLRH).

Effects of Whole Body Irradiation

The effects of acute whole body irradiation have been summarized in a number of articles.$^{2,6}$ Changes in the peripheral blood count secondary to bone marrow damage are manifest at all but the lowest doses (50 r or above). Data on human beings are inadequate to predict accurately the degree of effect to be expected in man. From considerations of the meager human data available, and from data on the various animal species studied, the time course of change in number of peripheral blood elements to be expected in human beings exposed to a single dose of penetrating radiation in the high sublethal range has been characterized as follows:$^5$ (1) The total white count increases during the first two or more days, then decreases below average levels. The total count then fluctuates over the next five or six weeks with no definite minimum and with some values above the pre-irradiation mean. The count becomes stabilized during the seventh or eighth week at low levels, and minimum counts probably occur at this time. A definite trend upward is apparent in the ninth or tenth week; however, complete recovery may require several months or more. (2) The neutrophil count parallels the total blood count. Complete return to pre-radiation values does not occur for several months or more. The initial rise in total white count is due to a neutrophilic leukocytosis. (3) The drop in lymphocytes is early and profound. Little or no evidence of recovery may be apparent several months after exposure, and return to pre-radiation levels may not occur for months or years. (4) The platelet count, unlike the fluctuating leukocyte count, falls in a regular fashion.
and reaches a low on the thirtieth day. Some recovery is evident early. However, as with the other elements recovery may not be complete several months after exposure. (5) As an index of severity of exposure, particularly in the sublethal range, the total white and neutrophil counts are of limited usefulness because of wide fluctuations and because several weeks may be required for depression to become evident. The lymphocyte count is of more value in this regard, particularly in this dose range, since depression occurs within hours of exposure. However, since marked depression of the lymphocyte count occurs with low dosage and since further increase in dose produces little more depression, this index is of little value at the higher doses. (6) Platelet counts show a regular pattern of change with the same time of maximum depression in all exposure groups and with the degree of depression roughly proportional to the calculated doses. It appears that the platelet count has considerable promise in the sublethal dose ranges as a convenient and relatively easy method of determining the degree of exposure.

**Gallium-72**

Gallium is in group III-B in the periodic table. Its atomic number is 31 and its average atomic weight, 69.72. It has several radioactive isotopes. Ga$^{72}$ was chosen because of its suitable half life of 14 hours. It is a bone seeker which emits beta rays with an average maximum energy of approximately 1.18 mev and several gamma rays. The gallium was administered i.v. as the citrate in a variety of dose patterns.

**Dosage Estimates**

Because of the non-uniform and rapidly changing local distribution of gallium in the body following injection, radiation doses received are difficult to calculate and therefore are difficult to interpret and compare with doses delivered by radiations from external sources. Thus the following are offered as orders of magnitude only: A dose of 1 µc. of Ga$^{72}$ per gram (60 mc. to a 60 Kg. man), if uniformly distributed and allowed to decay to infinity in the body, would deliver approximately 65 rads to deep tissues, of which approximately 74 per cent would result from gamma radiation and 26 per cent from beta radiation. Because of excretion, however (biologic half life of approximately 48 hours), this total dose is reduced to approximately 40 rads. Approximately 3/4 of the total dose is delivered in 24 hours.

**Clinical Studies**

All patients treated were suffering from advanced malignancy; some primary in bone, most metastatic to bone from either breast or prostate. All have received conventional therapy to the limit of effectiveness before admission to the BNLGH. In all, 21 patients were treated. Since the degree of hematologic effect to be expected with this isotope was not well known, therapy was given in what were considered to be moderate doses; and an interval between doses of two weeks was set arbitrarily in order to attempt hematologic appraisal between each dose. After it became apparent that the magnitude of hematologic depression could not be evaluated for at least four
HEMATOLOGIC FINDINGS AFTER THERAPEUTIC DOSES OF GA²⁸

weeks after a dose, longer intervals were established. Of the 21 patients treated, 11 died or left our care before complete hematologic appraisal was possible. In the remaining patients, despite variation in the total dose and in the dose rate, a general pattern of hematologic response was apparent even though there was considerable individual variation in response. This individual difference may, of course, be attributed in part to the nature and degree of dissemination of the malignant process and to prior therapy (deep x-ray), as well as to the variations in therapy. The following cases are presented as representative of the hematologic effects obtained.

Case 1. (C. L.) BNL No. 6025-R

This 36-year-old white female discovered a lump in her right breast 6 years before admission to BNLRH, and a radical mastectomy was performed one week later. She received no postoperative x-ray therapy and did well for 2 years. At this time she developed low back pain of gradually increasing intensity for which she was hospitalized, put into a body cast, and given deep x-ray therapy. Testosterone was administered for a period of 1½ years; however, progressive bony involvement requiring several periods of hospitalization for x-ray therapy occurred. Her last x-ray therapy was to the cervical spine one year prior to admission. Subsequent to this and up to her admission to the BNLRH she was bedridden at home and was treated with narcotics for pain. X-ray examination revealed diffuse metastatic bone involvement. She was given a single dose of 80 mc. of Ga²⁷ as the citrate i.v. Serial hematologic changes are portrayed in figure 1. An immediate fall in total WBC, paralleled by a fall in her absolute neutrophil and lymphocyte counts occurred following isotope administration. The nadir of the fall in total neutrophil and lymphocyte counts was reached at about 30 days after the treatment and was followed by a gradual return of the total WBC and the neutrophil count to normal levels at about the 60th day. On about the 70th day, an unexplained fever (probably due to a urinary tract infection) was associated with a pronounced leukocytosis of over 15,000 with a parallel rise in neutrophils. Her lymphocyte count remained low throughout, but rose temporarily to a normal range during the pleocytosis. Her total WBC was below 2,000 for 10 days. The response of her platelets was striking in that there was an interval of about 10 days following therapy during which the count was within normal limits. This was followed by a very abrupt fall in her platelet count again reaching a nadir at about 30 days, with a gradual recovery to normal levels at about the 80th day. This was followed by a secondary fall in platelets, with another low reached at 100 days from which there was no recovery until death. Minor evidence of bleeding during this latter period (3 episodes of epistaxis) were observed, but no gross bleeding despite a platelet count of under 50,000, lasting about 2 months.

Case 2. (M. G.) BNL No. 6241-R

This 38-year-old white woman noted a lump, which was believed to be benign, in her right breast 5 years before admission to the BNLRH. Two years prior to admission a lump appeared under her right arm, and the mass in the breast became larger. A biopsy was done followed by a radical mastectomy. She felt well until one year before admission, when she developed pain in both thighs and cutaneous metastases in the operative scar which were treated by x-ray. An oophorectomy was performed, which gave some relief from the pain and resulted in a further diminution in size of the cutaneous nodules. Six months before admission she developed severe pain in her neck, hips, legs, and back, for which she was given deep x-ray therapy to the spine over the succeeding months. On admission to the BNLRH, this patient received 2 doses of Ga²⁷ at 60-day intervals (fig. 2). A gradual fall in both the total white and the platelet counts, reaching a nadir between the 30th and 40th days, followed the first dose of gallium. These changes were less pronounced than in Case 1, and the platelets recovered more quickly than did the white count. A second dose on the 85th day produced a second fall in both elements, the platelets falling to 50,000 in about 39 days and the total white count to about 1,000 in 40 days. There was no evidence
of recovery from the platelet depression for the remainder of the patient's life. The platelet count remained at about 50,000 for 50 days and at 25,000 or less for 30 days. There was no gross bleeding during this time. Total white count fluctuated for the next 100 days but returned to the normal range shortly before death.

Case 3. (R. F.) BNL No. 6522-R

This 66-year-old white man, with a history of urinary obstruction and a prostatectomy 2 years before admission to the BNLRH, remained asymptomatic until 6 months prior to admission when he began to have pain in the pelvis and hips, a recurrence of dysuria and, on occasion, hematuria. Castration was performed 3 months before admission, with relief of pain for 2 months. Pain recurred and was present at admission to the BNLRH. X-rays showed diffuse involvement of spine, pelvis, and ribs.

This patient was given 50.0 mc and 65.5 mc. of Ga$^{67}$ at an interval of 2 weeks (fig. 3). There was an initial rise in total white and neutrophil counts, a pronounced elevation in circulating platelets, and a moderate fall in lymphocytes. Approximately 2 weeks after therapy, there was an abrupt fall in all the elements charted, which reached a nadir at about the 40th day. The total white and neutrophil counts rose slowly despite a subsequent dose of 50 mc on day 55, and fluctuated about a level somewhat lower than the initial count to reach normal levels shortly before death. The lymphocytes followed this same pattern. The platelet count behaved in an unexpected fashion. Following the third dose on day 55, there was a continued rise to day 72, followed by another fall reaching a nadir at day 85 with no further rise. The count remained at from 50–100,000 until death.

Case 4. (M. R.) BNL No. 5886-R

This 48-year-old white female discovered a lump in her left breast 3 years before admission. The breast was removed by radical mastectomy 2 weeks later. She received no postoperative x-ray therapy and did well for 18 months, after which she developed pain in her left thigh for which she received deep x-ray therapy. This gave relief for about 6 months but was then followed by pain in her left shoulder, back, hips, legs, and neck. She was given a sterilizing dose of x-rays 15 months before admission to the BNLRH. Six months before admission, x-ray therapy was administered to her clavicle, scapula, ribs, and
HEMATOLOGIC FINDINGS AFTER THERAPEUTIC DOSES OF Ga\textsuperscript{72}

Fig. 2.—Hematologic response to two doses of Ga\textsuperscript{72} with an 80-day interval between doses.

Fig. 3.—Hematologic response to Ga\textsuperscript{72} showing differences between responses of white cells and platelets to repeated doses.

ilium, and lower sacral area. Four months before admission a large dose of x-ray was delivered to her glenoid fossa on the right, and to the sella turcica. This was repeated a month later, and she was told that no further therapy could be given. She was ambulant with canes upon admission to the BNLRH, when gallium therapy was given. Her clinical response after therapy was surprising. Bone pain disappeared almost completely. She gained
weight and strength and discarded her canes, and on discharge 7 months after admission she contemplated a return to her previous occupation as secretary. There was no objective evidence of improvement in the bone metastases by x-ray. She did well for several months after discharge, but gradually developed a recurrence of bone pain for which she was hospitalized elsewhere. She again received deep x-ray therapy, followed by hematologic depression for which a number of transfusions were given until her readmission at the BNLRH.

Her hematologic response to therapy with Ga\(^{72}\) is shown in figure 4. She was given 50 mc initially and 85.5 mc at the end of 2 weeks. There was a rapid fall in the white and platelet counts beginning approximately 2 weeks after initial therapy and reaching a nadir in the fifth week. Her platelet count at this time was in the neighborhood of 25,000 and her white count ranged from 800 to 1,000. The depression of these elements lasted for about 9 weeks and was followed by a very gradual return toward normal over a period of months. On readmission to the BNLRH 8 months after discharge, she had 1,200 total white cells and 10,000 platelets. She began to bleed from the bowel and had massive melena almost daily for which she received in all 72 transfusions until death. These were of whole fresh blood, interspersed with platelet transfusions. For several days prior to death, no platelets were detectable in the circulating blood. Only on this patient was it possible to follow the depression of the red count with some clarity. There was a gradual fall in the red cell count, hematocrit and hemoglobin reaching a nadir at about 120 days, followed by a gradual return to pre-treatment levels over a period of similar length.

**DISCUSSION**

The cases presented were selected because they delineated most clearly the hematologic changes usually manifested in patients after administration of Ga\(^{72}\). The time course of change did not differ greatly from that indicated in the introduction for whole body external radiation; however, some differences were noted. An initial rise in white count was seen in some, but not all patients, as with external radiation. The neutrophil count paralleled the total
HEMATOLOGIC FINDINGS AFTER THERAPEUTIC DOSES OF GA$^{27}$

white count; however, the rate of fall after the initial rise was faster than with external radiation. The fluctuation in the total white count during this period, seen with the Marshallese$^2$ and the Los Alamos$^3$ accidents was not observed, indicating that the fluctuation seen with external radiation may have resulted from the relatively large, super-imposed doses of soft radiation to the skin. The time course of change in platelet count was remarkably similar to that reported for the Marshallese$^5$ and for patients given therapeutic total-body irradiation$^7$ except that an initial rise in platelet count was seen frequently in the present observations.

In the present report, total-body doses of the order of 75 or less rads were delivered. Yet, the hematologic findings are more commensurate with those seen following 150 or 200 r of external x- or gamma radiation.$^5,7,8$ In addition, a single patient at the BNLRH, given Na$^{24}$ orally in a dose calculated to yield approximately 75 r to the deep tissues in connection with therapy of a metastatic malignancy, did not show an appreciable degree of hematologic depression. These findings would tend to incriminate gallium, selectively deposited in bone and irradiating the marrow, as contributing to the greater degree of effect. Accurate data on gallium distribution as a function of time after administration in man are not available. Rat data$^1$ indicate that the degree of cortical bone deposition depends on the chemical amount of gallium administered. Under conditions for maximum bone deposition, the skeleton shows a significant degree of accumulation compared to other tissues. The skeleton, about 10 per cent of the body weight$^9$ had approximately 4 times the average concentration of Ga$^{32}$ for the entire body over the period of 12 to 48 hours after injection, and thus the dose rate to the marrow would be increased by this factor as a maximum. These data, of course, would not apply to man directly because of geometric and other differences; however, they may in part explain the severe degree of hematologic depression observed.

The secondary fall in platelets observed was reported in other studies$^5,7$ and appears to be a real phenomenon. It is possible to postulate several mechanisms to explain this effect. If attempts are made to explain it on the basis of rates of depression and regeneration in potentially dividing and maturing compartments at least two compartments in addition to that of the peripheral blood must be postulated. It was also noted that the pattern of change in the platelet count was more consistent than that of either the neutrophil or lymphocyte; for this reason it appears to be the most reliable hematologic index of the severity of radiation effect.

A second dose of gallium in these studies resulted in some patients in a more severe hematologic depression; in others, the degree of response did not seem to be affected markedly by the previous exposure. It is thus difficult to make statements regarding the rapidity and completeness of recovery. In this regard, patient No. 4 is of special interest. She had received an unusually large dose of deep therapy prior to the gallium and showed with Ga therapy a marked and sustained depression in all marrow elements from which recovery was very gradual. Apparently a very small marrow reserve and further deep x-ray therapy were sufficient to cause irreversible marrow failure, again, most manifest in platelet depression and uncontrollable hemorrhage resulting
in death. This would indicate that there are cumulative effects of radiation on the human marrow most manifest in platelet depression, with an ultimate point of no return. This, of course, implies the administration of very large doses. It may be that small doses produce changes from which recovery is complete. In addition, one must consider that the reaction of these patients to radiation has been influenced by the primary disease. This is undoubtedly so, but it would be expected to manifest itself, not by an alteration in the kind of response, but in its degree.

Of great interest to us, who had had little previous experience with patients having white cell counts in the range of 1,000 and platelet counts of 25,000 or less, was the absence of focal or generalized infection and the absence of gross bleeding, though epistaxis and purpura were common. The use of antibiotics was considered, but fear of infections with resistant organisms deterred this. In no case was bleeding sufficiently gross to require emergency transfusions except in Case 4.

**Summary**

The hematologic effects of Ga$^{72}$ administered intravenously to patients with diffuse bony metastases or primary bone malignancy were studied.

1. The effects of this internally administered isotope were, in general, similar to those resulting from total-body external radiation. The degree of effect was greater than that anticipated from estimates of the total-body dose received from the isotope. Localization in the bone may have been responsible for this finding.

2. The depth and duration of platelet count depression probably represented the best indices of the degree of marrow damage after radiation, and may be indicative also of the total damage sustained by the marrow from previous exposure.

3. The effects of large doses of radiation on the marrow appeared to be cumulative to a point of no return, beyond which regeneration may not be possible.

4. It was found that a total white count below 1,000 and a platelet count below 25,000 could be tolerated for weeks without infection or gross bleeding and with ultimate recovery. Therapy because of these findings alone did not appear to be indicated.

**Summario in Interlingua**

Esseva studiate le effectos hematologic de Ga$^{72}$ intravenose in patientes con diffuse metastases ossee o malignitate primari de osso. Es presentate le sequente constatationes.

1. Le effectos de iste isotopo in administration interne es generalmente simile al effectos de externe radiation del corpore integre. Le grado del effectos excedeva le expectation super le base de estimatos del dose recipite per le corpore integre ab le isotopo. Il es possibile que le localisation del isotopo in osso esseva responsabile pro iste constatation.

2. Le grado e le duration del deprimite numeration plachettal es le melior indices del grado de damno medullari post radiation e representa possibile-
HEMATOLOGIC FINDINGS AFTER THERAPEUTIC DOSES OF GA\textsuperscript{12} 873

3. Il pare que le efectos de grande doses de radiation super le medulla es cumulative usque a un puncto ubi omne regeneration comencia esser impossible.

4. Un total numeration leucocytic de infra 1\,000 e un numeration plachettal de infra 25\,000 pote esser tolerate durante plure septimanas sin infection o grossier grados de sanguination e con restablimento subsequente. Iste constataiones per se non representa un indication pro therapia hematologic.

REFERENCES
8. Nickson, J. S. and Bane, H.: Personal communication.
Hematologic Findings in Human Beings Given Therapeutic Doses of Gallium-72

W. WOLINS and V. P. BOND