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Joint Report of the Jilin ^{192}Ir Radiation Accident: A Clinical Study on A Case of Moderate Degree Bone Marrow Form of Acute Radiation Sickness with Extremely Severe Local Radiation Injury.

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Objective

After the medical handling of a patient exposed to extremely uneven total body irradiation from an 192Ir source (the activity was 2.765 TBq)on January 5,1996 in Jilin City, It is our hope to afford new experience and information for similar case in the future.

Methods

The dose distributions in the local tissues and the whole body were estimated by calculation. The biological doses were estimated by lymphocyte chromosome aberrations and micronuclei.

In order to save the life, eradicate the focus of infection and avoid the impending acute renal failure (a lesson learned from the Estonia radiation accident), his right lower extremity was amputated at the level of about 23 cm above the knee on day 8 and his left wrist amputated on the same day. 145 days after the exposure he had the 2nd amputation of his reserved right leg because of intolerable pain and failure of healing. Pathological examination of the amputated parts was made and dose (Gy) to the parts was estimated by electron spin resonance(ESR). The enzymes for muscle injury and HPRT gene mutation frequency (mf) were determined. The hemopoietic activity in the patients' sera was monitored The treatment consisted of strict isolation in laminar air flow room(LAFR),antibiotics, radioprotective agent, measures improving the micro- circulation and administration of rhG-CSF from day 4-23 with early recovery of leucocytopenia.

Results

The hemopoietic stem cell survival weighted whole dose was 2.9Gy,and the maximal skin surface dose estimation at the right lower leg extremity was 3737 8Gy The biological doses were consistent to the dose estimated by physical measurement. The local tissue absorbed dose estimated by ESR(Gy) at 1st amputated sites of femur were 45 4Gy and 38.4Gy respectively and at the 2nd amputated sites of femur were 9.1Gy,8.7Gy,6.6Gy and 6.5Gy respectively. There were GM-CSF-like,IL-3-like and Epo-like activities in the plasma of the patient and were consistent with the changes of WBC,RBC and Hb in the patient's blood The HPRT gene mf was determined to be 30x10-8,comparable to that of 3Gy 60Co r-rays in vivo and also consistent with the physical dose of 2 9Gy Massive necrosis of the cells of the epidermis, appendages of the skin ,hypodermis, skeletal muscles were seen microscopically in the heavily irradiated part of the right shank.

Conclusion

The authors emphasize the early amputation as the key to success, the importance of rhG-CSF effect and the significance of rational nutrition for the support of the patient, who had total body irradiation, massive local radiation injury and extensive surgical intervention to sustain

Key words ^{192}Ir Radiation accident, Acute radiation sickness, Amputation, Uneven irradiation

Description of the accident

On January 5,1996,at 7 40 in the morning, an unmarried young man worker(referred to as "Wen" hereafer)of 20 years old picked up a metallic cylinder with his left hand for about 15 inutes and put it with his right hand into his anterior pock of trousers below the knee and continued his duty. He began to vomit at 10·30 for several times. He took the factory bus at noon back to his dormitory for rest. He took off his trousers with radiation source in it and put it under his bed. At 17:00 an officer took away the radiation source so that he received irradiation for 9 hours and 20 minutes. The activity of 192Ir source for industrial radiography was 2 765 TBq.

Early clinical manifestation

He was treated at the local county hospital at 5:00 p.m. The first two WBC counts were 13 8x10^9/L(N:0.0,L:0 30) and 17 9x10^9/L(N·0.96,L·0.04),respectively. After administration of 10mg dexamethasone and some symptomatic treatment, the vomiting alleviated, but erythema was noticed at his left hand that night. Red swelling over his right lower extremity and left hand appeared on the following day with intolerable pain. A 0 8 cm2-sized bulla formed He was transferred to this hospital by air at 2p.m. 2 days post exposure.

The essential complaints and physical findings on admission were severe agonic expression, normal T,P,R and BP. No flushy face, no conjunctival congestion, nor swelling of the parotid glands.

Regional examination revealed red swelling below the level of left wrist associated with tenderness, warmth, pale skin with bulla at the deep part of the palmside, severe red swelling below the lower half of his right leg especially below the knee joint associated with warmth, hardness with elephantoid feeling on palpation; marked tenderness, especially at the lateral extensor side. A 0.8cm^2-sized bulla appeared at the anterior lateral side of right knee, also a dry erythema of 2x2cm^2 over the anterior surface of left lower leg

Blood examination: Hb156g/L,WBC14 3x10^9/L(N.0.97;L 0.03),platelet count 107x109/L,total lymphocyteson1-2 days postexposure:0.9x109/L-0 4x109/L

Whole body dose and local tissue dose estimated by physicist and biological dosimetrist

The whole body dose expressed by hemopoietic stem cell weighted dose is equivalent to 2 9+-0.3Gy and is shown in Table 1.

Table 1: Physical estimated doses

Level of anatomical transverse section	Dose(Gy)	Level of anatomical transverse section	Dose(Gy)
Center of head(frontal)	1.43	Subxyphoid	3.68
Center of orbit	1 62	7th thoracic vertebra	4.14
Center of oral cavity	1 84	2nd lumbar vertebra	4.55
4th cervical vertebra	1 61	3rd lumbar vertebra	4 90
7th cervical vertebra	1 82	5th lumbar vertebra	5.27
Subclavicular part	1.36	Pelvis center	5 73
2nd rib	2.36	Symphysis pubis, upper border	6.36
4th rib	2.82		
5th rib	3.25	Greater trochanter of femur	7.27

Whole body dose estimated by biological dosimetry (*Table 2*)

Table 2 : Dose estimated by biological dosimetry

	No.of cells	d+r	Rate of MN	Dose (Gy)
Chromosome	200(1)*	138		2.9(2 6-3.2)
Aberrations	350(2)*	270		3 09(2.88-3.28)
Micronuclei(CB)	287(3)*		50 17%	2 9(2 8-3.0)

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The whole body biological dose was also estimated to be 3 3-4.3Gy by LAP(neutrophils alkaline phosphotase)activity cytochemical stain.

Local tissue dose estimated by physicist(*Table 3*)

The reference dose estimated by thermoluminescence from watch ruby absorbed dose was 14.2Gy. Themaximal skin surface dose (3737 8Gy) at the right lower extremity was estimated by the nearest distance of source to skin as 2cm and the exposure time for 270 min.

Table 3: Local tissue absorbed dose estimation(Gy)

Location	Dose (Gy)		Exposure time
	Surface (skin)	Center (bone)	
Left wrist(8)*	13 0	10.5	15min
(10)*	8 3	6.2	15min
Pam of left hand	830.2	218 1	15min
Right lower extremity	3737.8	268.8	270min

* 8,10 denote the distance of 192 Ir sourse to the surface and center in cm, respectively

Table 4: Local tissue absorbed dose estimated by ESR(Gy)

Location of skeleton	Dose(Gy)		
	1st amputation site		2nd amputation site
	1st sample	2nd sample	
Amputated site of femur	45.4	36.5	9 1
	38.2	34.9	6.7
		27.4	6.6
		23.1	6.5
Amputated part of head	19.6		
of radius	15.9		
Remaining part of radius	12.0		
-after amputation	9.1		

*-measuring error 18%-22%

The 1st and 2nd amputations were performed at the level of 23 cm and 35 cm above the knee, respectively. All the bone samples taken from the different directions at the amputated sites were estimated by ESR method shown in Table 4 The 2nd bone samples from 1st amputated site and bone samples from 2nd amputation site were taken from four different directions,26cm and 35 cm above the knee, respectively

The clinical manifestations

The general course

"Wen" complained dizziness, nausea, anorexia and intolerable pain at the local radiation injury which must be relieved by analgesics The swelling of right lower extremity gradually extended to the middle of thigh upward and to the leg and feet downward, and the bullae at his left hand also extended He had a low grade fever of 37 C-37.9C. The general malaise and anorexia alleviated on the 6th post exposure day, denoting the passing of the disease into the apparent clinical well-being stage, but the local injuries deteriorated progressively It was decided to perform an early amputation of his right leg and left wrist on the 8th day post exposure in order to save the life The general conditions again aggravated on 16th day and he progressed into the critical stage with dropping of both white cell and platelet counts and the elevation of body temperature between 37 8C-38.2C He recovered into convalescent stage after the elevation of white cell count to 1.9x109/ L on day 21 On 57th day post exposure he was transferred to surgical ward for further treatment. 145 days after the exposure he had the 2nd amputation of his reserved right leg because of intolerable pain and lack of healing. The ulcer was resected and a moderate thisk skin was engrafted with ensuing healing of the ulcer without pain

The peripheral blood changes and bone marrow examination

After the relative great loss of blood during the 1st amputation, the Hb was dropped to the nadir of 55-71g/L as shown in Fig 1. The changes in white cell count after radiation are shown in Fig 2.

The changes in white cell and platelet counts of "Wen" are shown in Fig.3 and the changes in platelet counts of three relevant patients are shown in Fig.4.

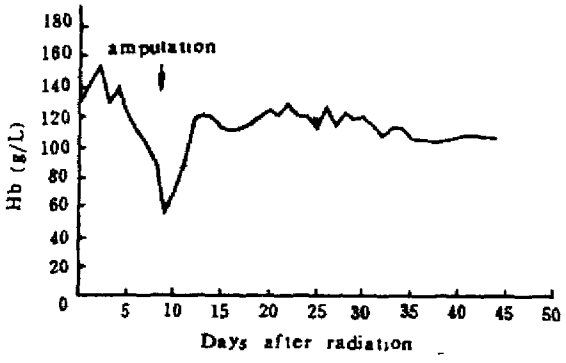

Figure 1: The changes of Hb post exposure in case "Wen"

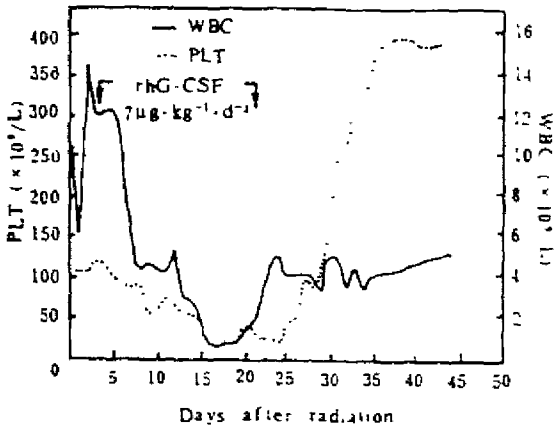

Figure 2. The total white cell count and platelet count changes post exposure in case "Wen"

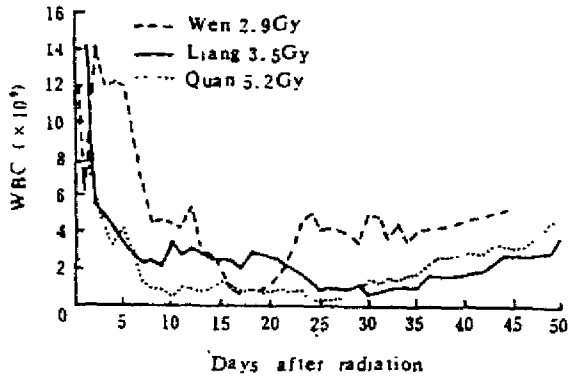

Figure 3: The comparison of total white cell count changes post exposure in 3 cases of bone marrow form of acute radiation sickness

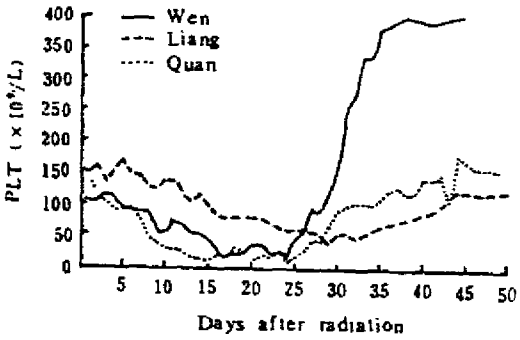

Figure 4: The comparison of platelet changes post exposure in 3 cases of bone marrow form of acute radiation sickness

The bone marrow changes and relevant examination (Table 5)

Table 5 : The bone marrow picture and relevant data

Days after irrad.	Cellularity	G:E	MK	MI. (%)	CFU-GM/ 2x105	CFU-E/ x105	BFU-E/ x105	CFU-MK/ x105	CFU-Mix/ x105
2	sl*hypo to normal	91:1	2	0	-	-	-	-	-
3	sl hypo	185.1	0	0	46 9± 2.2	76 3± 2.3	13± 1 8	3.06± 0.7	7 1± 0 7
7	normal	-	2	1	1 5.4± 0 3	32± 2	12± 1.2	0 3± 0.3	0 3± 0 3
14	severe hypo	36 1	0	0	0 11 5± 0.3	10± 1	1 5± 1 5	0.8± 0 8	3 1± 0 8
21	normal	4.1	10	1	1 65.6± 5.5	50± 3.3	10± 3.6	5.2± 0 8	13.3± 0 8
28	normal	39:1	0	0	95.2± 2.8	80.3± 2.3	75± 2.3	7.5± 0 7	11 5± 1.0
35	normal	2.6.1	43	4	184.0± 9 4	93 7± 3	80± 2.7	10± 0.7	13.7± 0 9

Evolution of local radiation injury

The reserved part of amputated right thigh developed again red swelling (day 15) and an 18x7cm sized bulla(day27) which healed on day 50. From day 78-109,the different sized residual erosion and necrosis were detected by echography and underwent debridement, and on day 145 2nd amputation of a section of right thigh 12cm upward was performed. The remaining part of the amputated left elbow healed up 14 days after the operation The radiation injury in the right hand was limited to the thumb and index finger with unhealed ulcer. The terminal phalange of the index finger had to be amputated and grafted with pedicle. Radiation injury at the left lower extremity was mainly limited to erythema, pigmentation vesicle and exudative ulcer along the inner side of left thigh close to the knee which were excised and succeeded in thick flap graft. The temperature changes shown by infra-red thermoimaging in detail are referred to Dr Yang's paper with figures in this issue

The assay of myocardial and musculature enzymes

The assay of myocardial and musculature enzymes is shown in Table 6

Table 6: Assay result of myocardial enzymes in "Wen"

Item	Normal value (U/L)	Time after exposure(day)						
		7	8	9	12	14	17	18
Glutamic oxalacetic transaminase (AST GOT)	<37	255	592	146	87	48	41	24
Lactate dehydrogenase (LDH-L)	96-214	482	361	180	193	166	108	115
Creatine phosphokinase (CK-NAC)	24-195	14430	8129	1649	450	92	52	38
Hydroxybutyrate dehydrogenase (HBDH)	95-250	383	311	149	196	170	110	104
Lactate dehydrogenase isoenzyme 1(LD-1)	10-50	66	36	24	27	51	30	24
Creatine phosphokinase isoenzyme MB(CK-MB)	<25	340	199	24	14	8	4	6

Musculature usually insensitive to irradiation. Massive destruction or irreversible damage to the muscles may cause release of a great amount of myocardial enzymes to the blood stream Ratio of CK-MB/CK-NAC, and LD-1/LDH-L are the criteria to differentiate the myocardial or musculature injury. The CK-MB isoenzyme occupies only 15% of total CK-NAC in myocardium. The CK-MB exceeding 6% of the total CK-NAC denotes myocardial injury, while a slight elevation of CK-MB but below 6% of total CK-NAC denotes musculature damage Similarly,LD-1 exceeding 17-27% of LDH-L or even higher denotes myocardial injury. The ratio of CK-MB/CK-NAC <6%,LD-1/LDH-L<17% with normal EKG and echocardiography in this patient denotes no myocardial damage. It is interesting to note that there was marked increase of CK-NAC on day 7 and day8 before the amputation.

Assay of hemopoietic activity in the patient's sera

By using the MTT method, investigation with some cytokine-dependent cell lines showed that there were GM-CSF-like,IL-3-like and EPO-like activities in the plasma of the patient and were consistent with the changes of WBC,RBCand Hb in the patient's blood. It might afford some experimental basis for rational clinical use of such cytokines.

The determination of N-acetyl-b-D-glucosaminadase(NAG) is the most sensitive and reliable test to monitor the renal function of patient with ARS and is superior to blood urea nitrogen(BUN)<creatinine(Cr) and uric acid(UA).

Immunological test: Decrease of rosette formation in the 1st week, severe inversion of T4/T8 ratio and nearly normal IgA,IgG and IgM throught the whole course of disease.

HPRT gene mutation frequency (Mf) was determined to be 30x10-8,comparable to that of 3Gy 60Co r-rays in vitro and also consistent with the physical dose of 2.9Gy. The mutation spectrum of HPRT gene was analyzed by multiplex PCR using 8 pairs of exon primers and showed exon deletion occurring in five of six mutants.

Treatment

Treatment in the prodromal and apparent clinical well-being stage

After total enviromental protection(TEP) and admission to LAFR,high calorie,high protein diet was supplied parenterally The high calories were supplied by carbohydrates and fat=the double energy, also the water-soluble and fat-soluble vitamins and minerals . Antibiotics such as penicillin,cefazolin and piperacillin were started from day 2 or day 4.

Treatment in the critical stage

The use of antibiotics continued for control of infection:cefobid (day 18-day 24) and amikacin (day 11-day38) were given,in addition to g-I nonabsorbable nystatin and iacontrozole Dicynone and reptilase as anti-hemorrage agents. 10mg albumin per day and 5g gamma-globulin every other day intravenously. Transfusion of 15 Gy irradiated blood and platelets before amputation.

Treatment in the convalescent stage stanozolol, iron preparation,folic acid and vitamin B12 were supplied to enhance the recovery.

Surgical treatment and anesthesia

In the procedures of two amputations of right lower extremity and one amputation for left wrist, general anesthesia was applied and the least possible loss of blood was pursued

Pathological characteristics of an extremely severe acute radiation injury in the legs and hands

Microscopically, massive necrosis of the cells of the epidermis, appendages of the skin, hypodermis, skeletal muscles were seen in the heavily irradiated part of the right shank, but the errector pili muscle was retained in the dermis. Vacuolar degeneration and massive necrosis of the cells of epidermis with extensive neutrophil infiltration were seen at the fingers and palm of left hand. Cysts of varying sizes were formed in the necrotic cells from dermis to part of epidermis There were degeneration and necrosis of glandular epithelial cells of sweat glands All the hematopoietic tissues in the upper end of the tibia and fibula. in the lower end of the femur, the radius and the ulna disappeared

Discussion and conclusion

Assessment of severity of the whole body irradiation

Judging from the lymphocyte counts on the 1st day and onset of vomiting about 3 hours after the exposure, it was probably a case of moderate degree acute bone marrow radiation syndrome clinically; the absorbed dose was later estimated by physical dosimetrist, lymphocyte chromosome aberrations and micronuclei to be 2.9Gy hemopoietic stem cell survival weighted whole body dose..

Early amputation of the heavily irradiated right lower extremity and left wrist was the key to success. The highest local radiation dose at the right leg was 3737.8Gy which was much higher than that in Estonia radiation accident The massive necrosis of that part might become the focus of the severe infection very difficult to handle and also the absorbtion of the toxic substance was the impending threat of acute renal failure The level of amputation was judged by the physical dose estimation and also the clinical demarcation of the skin lesions

The evaluation of the early use of rhG-CSF effect: we have our own experience in ARS in the recent use of GM-CSF when the white cell counts were below 1x109/L and attained the effect of shortening of the period of leucopenia below 1x109/L for about 7 days in comparison with similar degree of irradiation.

In this case, the patient received major amputation of his right lower extremity with great loss of blood reflected in the drop of Hb to 55g/L on about day 10. The simultaneous loss of white cells and platelets could not be overlooked so that there was an early drop of leucocytes to the nadir of 0.65x109/L and platelets to the nadir of 19x109/L both at day 17.

The significance of rational nutritional support for the patient

Nutrition is very important in this case with whole body irradiation, massive local radiation injury and rather major amputation to sustain..

Thromoboelastography may not only be used to study the mechanism of platelet function in blood coagulation,but also have the prospect to afford a method for dose estimation.