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CHROMOSOME ABERRATIONS IN CIRCULATING LYMPHOCYTES AFTER BRACHYTHERAPY FOR UTERUS CARCINOMA

Studies on chromosome aberrations in circulating blood lymphocytes from patients treated for cancer disease by external or internal exposure can serve two purposes: a) they can simulate the situation after an accidental inhomogeneous irradiation and thus aid the assessment of biological damage in such situations, b) they can help to evaluate the response of the patient to the therapy and, possibly, discern patients of abnormal radiosensitivity. Several such studies were carried out in our laboratories in the past, investigating patients with mammary cancer (1, 2), pelvic cancer (3), brain cancer (4) or thyroid cancer (5)—the latter after treatment with ^{131}I. The present study deals with chromosome aberrations in ten patients before and after ^{137}Cs brachytherapy for uterus cancer.

Material and Methods. The investigation was carried out on 10 patients, aged from 37 to 91 years, suffering from cervical cancer, corpus uteri cancer stage 1 or 2a or cervical dysplasia (Table). The patients had not been treated previously. The intracavitary ^{137}Cs treatment involved one cylindrical applicator in the uterine cavity (consisting from the fundus downward of 3 sources of 1.4, 0.814 and 0.814 GBq) and two olive-shaped applicators (1.34 GBq each) placed laterally in the vaginal vault. The duration of exposure and the calculated dose at point A (a point defined by the brachytherapy protocol as being situated 2 cm above the lateral applicator and 2 cm to the side from the cervical midline) are given in the Table. Obviously, this treatment yields very inhomogeneous doses at low dose rates. Blood samples (0.5 ml) were taken before and 1 day after termination of the treatment; they were cultured in 5 ml of F-10 Ham's medium in the presence of fetal calf serum, phytohemagglutinin and antibiotics at 37°C. One ml of 10^{-5} M

Table

Cytogenetic observations in patients before and after treatment

Patient No.	Sampling	Dose Gy (hours exposed) tumor & stage)	No cells analyzed	No abnormal cells	Type and Number of aberrations		
					Chromatid		
					Gaps	Breaks	Exchanges
1	Before	52.5 (70 h)	200	2	0	0	0
	After	Cerv. C. T1	300	20	2	0	0
2	Before	52.5 (70 h)	200	1	1	0	0
	After	Cerv. C. T1NXM0	300	23	3	0	0
3	Before	60 (80 h)	200	5	0	1	0
	After	Copr. C. T1NXM0	300	14	0	2	2
4	Before	30 (50 h)	200	2	2	0	0
	After	Cerv. D.	300	10	2	0	0
5	Before	50 (67 h)	200	8	4	0	0
	After	Cerv. C. T1NXM0	200	10	3	0	0
6	Before	50 (67 h)	200	1	0	1	0
	After	Cerv. C. T1NXM0	200	22	1	9	0
7	Before	50 (67 h)	185	4	0	0	0
	After	Cerv. C. T2aNXM0	200	16	2	1	0
8	Before	50 (67 h)	200	6	2	0	0
	After	Cerv. C. T1NXM0	200	16	2	3	0
9	Before	50 (83 h)	200	5	1	2	0
	After	Cerv. C. T1NXM0	200	18	3	0	1
10	Before	50 (50 h)	200	7	3	1	0
	After	Copr. C. T1NXM0	200	11	1	0	0

Abbreviations: Cerv. C. = cervix carcinoma; Cerv. D. = severe cervix dysplasia; Corp. C = corpus two olive-shaped applicators in the vaginal vault

colchicine was added after a culture period of 45 h, and the culture was continued for a total of 48 h. Metaphase slides were prepared and stained in the usual way as described previously (6). In general, 200–300 metaphases were examined for different types of chromosome aberrations (Table).

Results. The results presented in the Table show a moderate increase in chromosome aberrations after irradiation, in particular dicentrices and rings. Thus dicentrics + rings increased from an average pre-irradiation level of 0.5/100 cells to 3.9/100 cells. When the increase in dicentric aberrations after irradiation is adjusted to a nominal dose of 50 Gy, a yield of 3.5 ± 0.6 dicentrics/100 cells (Poisson error) was obtained. A deviation from the Poisson distribution was detectible only in patient No. 4 exposed for 50 h to a nominal dose of 30 Gy. Fewer aberrations were found after irradiation in the lymphocytes of patients No. 3 and No. 5 than in those of the other patients, but a comparison of the calculated standard deviations of the increase in dicentrics + rings with and without these patients included (1.5 and 0.993) and the only moderate discrepancy from that of the Poisson distribution did not seem to justifiy the assumption that patients differ in their individual susceptibility to radiation. The radiation-induced increase found in dicentrics + rings could be compared with the dose effect curve obtained earlier (7) for ^{60}Co gamma irradiation in vitro. This yields an estimate for the average whole body dose of about 0.5 Gy. However, due to the low rate and the intervening repair of sublethal damage, few dicentrics will result from the interaction of two independent radiation tracks, and the dose-square coefficient of the dose-effect relationship can be neglected (8, 9). Using only the linear parameter of the dose-effect relationship, one obtained a whole body dose estimate of about 0.8 Gy. For patient No. 4, the 'contaminated Poisson distribution method' (10) could be used to determine dose and part of the body exposed yielding a dose estimate of 3.5 Gy to 10% of the body.

Discussion. The observations presented raise two interesting questions. Firstly, the dose estimate of 0.8 Gy averaged over the entire body appears reasonable in view of the fact that the total volume does is about 60 J or about 1 Gy for a person weighing 60 kg. Secondly, the fact that there is no deviation from the Poisson distribution for longer exposure periods in all patients except one patient indicates that the lymphocytes sampled after exposure passed through the radiation field in a fairly homogeneous manner during the exposure, and that few lymphocytes seemed to have entered or left the circulation during this time. This situation differs markedly from that encountered after a single short-time exposure form an acute accidental exposure or from conventional external radiation therapy where the deviation from the Poisson distribution allows to estimate the percentage of the body exposed. An alternative explanation that damaged cells are preferentially removed seems unlikely because, in general, in vivo and in vitro dose effect curves match well and because, for acute inhomogeneous exposure, the contaminated Poisson distribution gives reasonable results. The observation of a homogeneous exposure of lymphocytes during a ≈ 2 day dose protraction is also of interest with respect to the life cycle of lymphocytes and requires further follow-up for longer periods of time after exposure.

From the results one can conclude that the method of the 'contaminated Poisson distribution' will not add any useful information with respect to percentage of body exposed when applied to low dose rate inhomogeneous exposure, for example, due to accidents involving lost or stolen radioactive industrial or medical sources (11).

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with ^{137}Cs brachytherapy for uterus carcinoma or dysplasia

observed				Distribution dicentics + rings/cell		
Chromosome						
Breaks	Translocat.	Rings	Dicentrics	0	1	2
1	0	0	2	198	2	0
4	0	1	14	286	13	1
0	0	0	0	200	0	0
4	2	0	14	286	14	0
2	0	0	2	198	2	0
4	0	1	7	292	8	0
0	0	0	0	200	0	0
2	0	0	8	295	2	3
4	0	0	2	198	2	0
2	1	0	4	196	4	0
0	0	0	0	200	0	0
11	0	0	6	194	6	0
2	1	0	1	184	1	0
5	0	0	8	193	6	1
4	0	0	1	199	1	0
1	0	1	9	190	10	0
2	0	0	0	200	0	0
4	0	0	12	189	10	1
2	0	0	2	198	2	0
3	0	0	8	192	8	0

carcinoma). Patient No 4 was treated with a cervical applicator only; all other patients had in addition

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