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Malignant Melanoma: Sex Differences in Response to Chemotherapy?

F. H. J. RAMPEN*
Rotterdamsch Radiotherapeutisch Instituut, Rotterdam, The Netherlands

Abstract—*From studying cell kinetic parameters it is demonstrated that both males and females with metastatic melanoma respond favourably to various chemotherapy schedules. Male patients have a shorter doubling time (DT) of pulmonary secondaries prior to chemotherapy compared to females, which seems to give them a less favourable starting point. Also, the DT of lung metastases of males after chemotherapy is less favourable than that of females. However, a significant difference in DT is noticed between measurements prior to and after the institution of chemotherapy in both sexes. It is concluded that the alleged sex differences in response to chemotherapy may be an artifact due to differences in tumour growth kinetics between males and females.*

INTRODUCTION

FEMALES with malignant melanoma experience a more favourable response to chemotherapy than males [1]. A possible explanation of this phenomenon is the slower growth rate in females of melanoma secondaries, as expressed in a longer tumour volume doubling time (DT) and in a longer survival after first evidence of distant metastases [2, 3]. The present investigation was designed to determine the DT of pulmonary metastases in male and female patients receiving chemotherapy. The results are compared with pre-treatment DT measurements.

MATERIALS AND METHODS

From 688 patients with biopsy-proven cutaneous melanoma, registered at the Rotterdamsch Radiotherapeutisch Instituut between 1956 and 1978, 98 had documented pulmonary secondaries. From these, the DT of the lung metastases was determined from the available chest X-ray films. Fifty-four patients were excluded for various reasons (Table 1). Patients with lentigo maligna melanoma were not considered because of the distinct behavioural characteristics of this histological type [4]. Contiguity with the mediastinal structures or with the thoracic wall precluded accurate appraisal of changes in tumour volume. The same applied to lesions with indistinct margins. The minimum time span over which serial films were considered reliable for DT estimation was 14 days. Patients who received chemo- or immunotherapy less than 3 months before the appearance of secondaries on the chest roentgenogram were also excluded. Serial X-rays of each patient appeared similar as to the size of the bony chest, indicating congruency of radiological techniques.

Of 44 eligible patients, 31 were suitable for accurate DT measurements without, or prior to, chemotherapy (20 men, 11 women). The growth rate under chemotherapy could be determined in 25 instances (14 men, 11 women). In 12 patients, DTs were calculated both before and after the institution of chemotherapy (8 men, 4 women).

Caliper-based tumour volumes (V) were obtained from the formula:

$$V = \frac{4}{3}\pi\left(\frac{a+b}{4}\right)^3,$$

where a represents the maximum tumour diameter and b the perpendicular diameter.

Table 1. Patients excluded from analysis

Lentigo maligna melanoma	5
Only 1 X-ray with metastases available	11
Lesions in contiguity with the mediastinal structures or the chest wall	10
Indistinct lesional contours	16
Pulmonary secondaries discovered at autopsy	2
Chemotherapy within 3 months prior to the appearance of lung metastases	3
Time lapse between serial films less than 14 days	1
Second primary malignancy	1
X-ray films not available (performed elsewhere and destroyed)	5
Total	54

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*Present address: Academisch Medisch Centrum, Meibergdreef 9, Department of Dermatology, 1105 AZ Amsterdam, The Netherlands.

The DTs were derived from the following equation:

$$DT = \frac{t \log 2}{\log V_t - \log V_0},$$

where V_t represents the tumour volume at time t (last X-ray) and V_0 the initial tumour volume [5]. Since multiple metastases in the same patient often exhibit different growth rates, V_0 and V_t were determined by totalling the volumes of all measurable pulmonary deposits. The range of the number of metastases in patients without therapy was 1–28, whereas patients receiving chemotherapy had 1–16 pulmonary lesions. When more than 2 radiographs were available for pre-treatment DT assessment, only the first and last films were ascertained. In treated cases a time span of 2 months after the initiation of chemotherapy was considered suitable for response assessment. Thus, where appropriate, the first X-ray film after a 2-month period of chemotherapy was used as the latter film for DT calculation.

RESULTS

Both females and males showed a favourable response to chemotherapy. All DT results of male and female patients, both with and without chemotherapy, are depicted in Fig. 1. Out of 14 treated males, at least 6 experienced a definite regression of their pulmonary

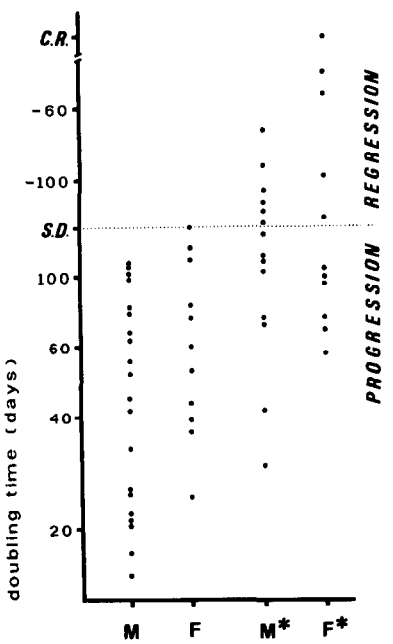

Fig. 1. DTs of pulmonary metastates in male (M) and female (F) patients. The DTs prior to, or without chemotherapy are depicted in the first two columns, whereas the post-treatment DTs are shown in the last columns (asterisk).

secondaries, as expressed by a 'negative' DT. It is important to emphasize that a 'negative' DT represents the time necessary for a given tumour volume to be reduced to half the original volume. Only one male patient was clinically documented as showing a partial response (PR, ≥ 50% tumour regression). Of the 11 treated females, 5 showed tumour regression. The case notes mentioned only one complete response (CR) and two PRs. Both categories of females fared better than the corresponding groups of males, although the differences were not statistically significant ($P > 0.10$, Wilcoxon test). The differences in DT between the male patient groups with and without chemotherapy were highly significant ($P < 0.01$). For the female groups a significant difference was also observed between pre-treatment and post-treatment DTs ($P < 0.02$).

Table 2 shows the treatment details and the DTs of all patients studied. Treatment schedules varied considerably according to the protocols in vogue at the time of treatment. There was no distinct discrepancy in therapy regimens between the male and female groups. In 12 instances the pre-treatment DT could be compared with the post-treatment DT in the same patient: in all but two (male) patients the post-treatment DT was longer, or negative, as compared with the pre-treatment DT. Thus, 6 out of 8 male patients experienced a favourable influence of chemotherapy on tumour growth. A discrepancy was noticed in the age distribution between the treated and untreated categories. In the latter group 12 out of 19 patients were 60 yr or older, compared with only 3 out of 25 in the treatment category. However, this did not influence the results, since age as such was not correlated with DT.

DISCUSSION

Studies on cell kinetics and survival of melanoma patients are very rare. Previously, we have studied the growth rate of pulmonary metastases in male and female melanoma patients who did not receive any form of therapy and we noticed that men had more rapidly growing secondaries than women [3]. An endocrine influence on the growth kinetics of melanoma was therefore hypothesized, warranting the design of anti-androgenic treatment schedules, particularly in male patients with metastatic melanoma [2, 3]. The present study lends further support to the theory that malignant melanoma may represent a hormone-dependent tumour.

On the whole, fast-growing tumours exhibit a more favourable response to chemotherapy

Table 2. Doubling time of pulmonary metastases in melanoma patients with and without chemotherapy

	Sex/age		Without chemotherapy			With chemotherapy			
			No. of metastases	Time span (days)	DT (days)	Regimen (No. of courses)	No. of metastases	Time span (days)	DT (days)
1	M	69	3	14	10.3				
2	M	65	5	28	15.1				
3	M	48	2	83	20.3				
4	M	60	1	96	21.7				
5	M	33	1	87	24.0				
6	M	36	4	102	41.5				
7	M	87	28	168	44.4				
8	M	65	1	92	51.3				
9	M	37	2	120	54.7				
10	M	71	3	84	63.2				
11	M	71	2	65	97.8				
12	M	28	1	263	104.2				
13	F	72	1	15	23.8				
14	F	61	1	68	39.4				
15	F	48	1	39	43.5				
16	F	82	2	167	51.8				
17	F	69	2	189	59.9				
18	F	65	1	400	79.7				
19	F	53	1	16	SD				
20	M	41				DTIC + BCNU + vincristine (2)	1	52	28.5
21	M	53				DTIC + BCNU + vincristine (3)	3	58	69.8
22	M	64				DTIC + *Corynebacterium parvum* (2)	3	63	111.6
23	M	57				Methyl-CCNU (2)	16	81	143.4
24	M	57				Methyl-CCNU (1)	1	34	146.2
25	M	56				DTIC + *Corynebacterium parvum* (3)	2	97	−139.0
26	F	55				DTIC (2)	7	63	57.5
27	F	32				DTIC + *Corynebacterium parvum* (1)	5	37	67.7
28	F	56				Hydroxyurea + cytosine arabinoside (2)	8	34	73.1
29	F	37				DTIC + vincristine (1)	2	40	100.3
30	F	69				DTIC + vincristine (2)	4	82	112.2
31	F	36				CCNU + vincristine + bleomycine (1)	2	42	−97.3
32	F	27				DTIC + BCNU + vincristine (3)	1	99	CR
33	M	61	1	143	20.7	Melphalan (2)	1	30	−90.3
34	M	44	7	32	24.1	DTIC + *Corynebacterium parvum* (4)	3	83	−69.4
35	M	49	2	15	32.3	DTIC (2)	2	36	−361.2
36	M	32	2	150	66.4	DTIC + BCNU + vincristine (3)	2	101	253.3
37	M	59	2	63	75.9	DTIC + BCNU + vincristine (1)	2	56	−168.6
38	M	50	6	93	77.8	Mitomycin C (1)	6	26	−156.5
39	M	56	2	84	109.9	DTIC + *Corynebacterium parvum* (3)	3	62	41.5
40	M	38	4	309	110.7	Cytosine arabinoside (1)	1	22	73.6
41	F	35	1	150	35.8	DTIC (2)	2	42	−48.6
42	F	52	2	186	72.7	DTIC + *Bacillus Calmette-Guerin* (2)	2	106	93.9
43	F	43	1	589	144.5	Methyl-CCNU (2)	2	69	−35.8
44	F	37	1	359	216.1	DTIC (2)	1	54	−270.9

The time span indicates the period over which serial X-rays were examined for growth-rate assessment.
SD = Stable disease; CR = complete response.

than more slowly growing tumours. The general observation of a better response to chemotherapy in women as compared to men [1], and the results reported here, which show a faster pre-treatment growth rate in male patients against a less favourable response to chemotherapy, seem to contradict the above-cited rule. However, when the pre-treatment DTs are taken into account a significant difference is encountered between the DTs in both men and women with chemotherapy and the DTs without, or prior to, chemotherapy. Stated another way, the response to chemotherapy is more or less the same in male and female patients, although the absolute response appears better in females, simply because females seem to have a more favourable starting point. The general impression that males

respond less favourably to chemotherapy than their female counterparts could not be borne out by the present investigation: the response relative to the pretreatment growth rate was basically similar in both sexes. Thus, it is, rather, the difference in DT between males and females that pretends a more favourable response to chemotherapy in females.

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