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P. J. M. Sessink · E. D. Kroese · H. J. van Kranen
R. P. Bos

Cancer risk assessment for health care workers occupationally exposed to cyclophosphamide

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Abstract In the present study a cancer risk assessment of occupational exposure to cyclophosphamide (CP), a genotoxic carcinogenic antineoplastic agent, was carried out following two approaches based on (1) data from an animal study and (2) data on primary and secondary tumors in CP-treated patients. Data on the urinary excretion of CP in health care workers were used to estimate the uptake of CP, which ranged from 3.6 to 18 μg/day. Based on data from an animal study, cancer risks were calculated for a health care worker with a body weight of 70 kg and a working period of 40 years, 200 days a year (linear extrapolation). The lifetime risks (70 years) of urinary bladder cancer in men and leukemias in men and women were found to be nearly the same and ranged from 95 to 600 per million. Based on the patient studies, cancer risks were calculated by multiplication of the 10-year cumulative incidence per gram of CP in patients by the estimated mean total uptake in health care workers over 10 years, 200 days a year. The risk of leukemias in women over 10 years ranged from 17 to 100 per million using the secondary tumor data (linear extrapolation). Comparable results were obtained for the risk of urinary bladder tumors and leukemias in men and women when primary tumor data were used. Thus, on an annual basis, cancer risks obtained from both the animal and the patient study were nearly the same and ranged from about 1.4 to 10 per million. In The Netherlands it is proposed that, for workers, a cancer risk per compound of one extra cancer case per million a year should be striven for ("target risk") and that no risk higher than 100 per million a year ("prohibitory risk") should be tolerated. From the animal and the patient study it appears that the target risk is exceeded but that the risk is still below the prohibitory risk.

Key words Antineoplastic agents · Biological monitoring · Occupational exposure · Cyclophosphamide · Cancer risk assessment

P. J. M. Sessink (✉) · R. P. Bos
Department of Toxicology, Faculty of Medical Sciences, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

E. D. Kroese · H. J. van Kranen
Laboratory of Carcinogenesis and Mutagenesis, Institute of Public Health and Environmental Hygiene, P.O. Box 1, 3720 BA Bilthoven, The Netherlands

Introduction

Antineoplastic agents are widely used in the treatment of cancer and some non-neoplastic diseases [5, 6]. Depending on their mechanism of action, these drugs are subdivided into several categories, e.g., alkylating agents, antimetabolites, mitotic inhibitors, and antibiotics. The alkylating agents express their cytotoxicity by interaction with the DNA of tumor cells. Because the desired cytotoxicity is not specific for cancer cells, normal cells may also be damaged, resulting in toxic side-effects. Carcinogenicity of a number of antineoplastic agents has been observed in animal studies and primary and secondary tumors have been found in patients treated with these drugs [4, 10, 11, 13–17, 21]. Cyclophosphamide (CP) is one of the most frequently used alkylating antineoplastic agents for different types of tumors [5, 31]. According to the International Agency for Research on Cancer, there is sufficient evidence of carcinogenicity in humans and animals [13, 14]. Due to its reactivity with DNA and mutagenicity in various short-term tests, CP is classified as a genotoxic carcinogen.

Because of the carcinogenic potency of CP and other antineoplastic agents, health care workers involved in the preparation and administration of these drugs may be at risk [30]. Therefore exposure to these compounds should be avoided, and safety guidelines and protective

measures such as wearing masks, gloves, gowns, and special clothes and using laminar air-flow safety hoods have been introduced to protect workers when handling these drugs [1, 29]. Nevertheless, in several studies it has been shown that uptake of CP does occur during occupational activities [24, 25, 27, 28]. With a sensitive gas chromatographic-mass spectrometric method CP has been detected in the urine of health care workers handling antineoplastic drugs [26].

The risk of exposure to CP and other antineoplastic agents has been discussed in many studies [7, 9, 32]. However, a quantitative risk assessment could not be made because of the lack of the necessary exposure data. In this study we used data on the urinary excretion of CP in health care workers to estimate the uptake of CP. Next, a cancer risk assessment was carried out following two approaches based on (1) data from an animal study and (2) data on primary and secondary tumors in CP-treated patients.

Although we realize that risk assessment of occupational exposure to carcinogens is a complex matter, we think that such data are necessary to set priorities in the protection of workers against genotoxic carcinogens. In this paper we present an initial approach to cancer risk estimation for health care workers exposed to CP. The pitfalls are discussed.

Materials and methods

Carcinogenicity studies in animals

Carcinogenicity of CP has been observed in several animal studies [13, 14, 21]. For cancer risk assessment, studies are needed in which the animals are chronically exposed to at least two doses, preferably giving a clear dose-response relationship. Only the study of Schmähl and Habs appears to satisfy this requirement [20]. In this study male and female Sprague-Dawley rats were treated with CP in drinking water. The treatment started when the rats were 100 days old. Doses of 0, 0.31, 0.63, 1.25 and 2.5 mg/kg body weight were administered, 5 times a week, during their lifetime. Forty rats were used for each sex and dose. After a lifetime observation period, tumors of the urinary bladder and of the lymphoid and hematopoietic tissues (leukemias) were most frequently found and a dose-response relationship was obtained (Table 1). A statistically significant increase in leukemias was observed in males and females combined. Only in males was a statistically significant increase in tumors of the urinary bladder found.

Table 1 Urinary bladder tumors and leukemias from oral cyclophosphamide treatment in male and female Sprague–Dawley rats[a]

Dose 5 times of week (mg/kg body weight)	Number of urinary bladder tumors		Number of leukemias
	Males	Females	Males and Females
0	0/38	0/34	0/72
0.31	2/34	0/37	3/71
0.63	2/36	0/37	6/73[b]
1.25	5/35[c]	0/33	6/68[d]
2.5	7/31[e]	1/27	4/58[f]

[a] From Schmähl and Habs [20]
[b] Fischer exact test: $P = 0.015$
[c] Fischer exact test: $P = 0.022$
[d] Fischer exact test: $P = 0.011$
[e] Fischer exact test: $P = 0.0024$
[f] Fischer exact test: $P = 0.037$

Epidemiological studies in patients

Many cases of cancer have been reported after therapeutic treatment with CP [4, 10, 11, 13, 14, 16, 17, 21]. Among the various types of cancer, leukemias and tumors of the urinary bladder have been found most frequently not only as secondary tumors following cancer treatment but also as primary tumors after treatment for non-neoplastic diseases. In some of these studies the doses of CP were known and consequently the relative risks could be calculated [11, 17]. The results of these studies showed a dose-dependent increase in the relative risk of developing leukemias after treatment with CP for breast and ovarian cancer. For cancer risk assessment only data can be used from studies in which, in addition to the dose of CP administered, the tumor incidence is given. Both kinds of data were available, from two studies and these are briefly described below [4, 10].

In five clinical trials the development of secondary leukemias was studied in 333 ovarian cancer patients treated with CP [10]. For the total group, a 10-year cumulative incidence of 5.4% was calculated. When the total group was subdivided into three dose groups, only in the highest dose group were leukemias observed, with a 10-year cumulative incidence of 11.1%. For 1657 ovarian cancer patients not treated with CP a 10-year cumulative incidence of 0.1% was found.

The development of tumors was also studied in patients with rheumatoid arthritis treated with CP as an immunosuppressive agent [4]. A total of 119 patients (76 women) were treated with a mean CP dose of 52.9 g while 119 matched controls received no CP. Tumors were observed in 24.4% of the CP-treated patients during an observation period of 10.8 years. A tumor incidence of 13.4% was observed in the matched controls during an observation period of 11.8 years. An increased incidence was observed for urinary bladder tumors (6 vs 0), skin cancer (8 vs 0) and leukemias (5 vs 1). The proportion of patients with tumors was significantly higher among men than women in the CP-treated group and in the control group. The increase in tumors between the control group and the CP-treated group was the same for men and women. Unfortunately, no information was available on sex-specific tumor types.

Estimation of the daily uptake

Despite the introduction of safety guidelines and protective measures, in several studies it has been shown that (health care) workers involved in the preparation and administration of antineoplastic agents like CP are exposed to this particular compound, since uptake was established by detection of CP in urine (Table 2) [8, 12, 24, 25, 27, 28]. In order to avoid the use of unreliable data obtained from urinary CP excretion after a rather short period of only a few days, urine of eight hospital pharmacy workers was collected during two to four periods of 4 successive days. A total of 476 urine samples were analyzed. CP was detected in one or more urine sample of each worker. The mean daily excretion was 0.18 μg (range: 0.01–0.53 μg). These urinary excretion levels are the basis for the estimation of the exposure. In urine samples with undetectable amounts of CP the amounts excreted were set at zero.

It is supposed that during occupational activities antineoplastic agents like CP are absorbed by inhalation and via dermal penetration [2, 12, 18, 27]. Such exposure conditions were imitated in rats by

Table 2 Range of cyclophosphamide in urine of (health care) workers exposed to antineoplastic agents

Group	No. of workers	Period of urine sampling (days)	Mean amount[a] (range) of CP in urine (μg/day)	Reference
Health care workers	20	4	0.39 (0–2.5)	Evelo et al. [8]
Nurses	2	57[b]	0.47 (0.43–0.51)[c]	Hirst et al. [12]
Pharmacy technicians	2	2	0	Sessink et al. [23]
Pharmacy technicians	25	1–2	0.05 (0–0.5)	Sessink et al. [24]
Animal caretakers	4	2–5	0.05 (0–0.2)	Sessink et al. [25]
Pharmacy technicians[d]	9	1–2	1.36 (0–10.05)	Sessink et al. [27]
Pharmacy technicians[d]	9	5	0.16 (0–0.51	Unpublished
Nurses	8	1	0.79 (0–2.9)	Sessink et al. [28]
Pharmacy technicians	1			
Cleaning women	2			
Nurses	7	2–4	0.80 (0–4.2)	Unpublished
Pharmacy technicians	8	8–16	0.18 (0.01–0.53)	This study

[a] Amounts below the detection limits were set at zero
[b] In both nurses urine sampling was performed over a total of 57 days
[c] Mean and range were calculated by assuming a mean sampling period of $28\frac{1}{2}$ days
[d] The same persons

intratracheal instillation and dermal application of a single CP dose of 1 mg/kg body weight [22]. For both treatments a total of about 5% of the applied dose was excreted unchanged in urine, all within 24 h. Application of 1 mg CP on the skin of volunteers revealed a urinary excretion of about 1% [12]. The mean uptake of CP was calculated by multiplication of the mean daily urinary CP excretion of 0.18 μg by 20 (5% excretion after dermal and intratracheal treatment of rats) or 100 (1% excretion after dermal application in volunteers). Hence, it was estimated that the mean daily uptake of CP will range from 3.6 to 18 μg.

Cancer risk assessment based on the animal study

Cancer risks were estimated using linear extrapolation and assuming that the time dependence of tumor development is more likely related to the cumulative dose of CP than to life span and the rate of aging [19]. The model is based on intersection of a straight line between zero dose and the lowest dose in the animal experiment at which a significant increase in tumors is observed (Table 1). From the results of the study of Schmähl and Habs, the inedian survival periods of the rats at the different doses were obtained [20]. To calculate the exposure periods, the survival periods were reduced by 100 days (at the start of the experiment the rats were 100 days old) and multiplied by 5/7 (the rats were administered CP 5 times a week). The total cumulative CP doses were calculated by multiplication of the doses by the exposure periods. The cancer risks per mg CP were calculated by dividing the tumor incidences by the total cumulative CP doses. Finally, lifetime cancer risks for health care workers were calculated by multiplication of the cancer risks per mg CP in rats by the total cumulative CP uptake of the health care workers over a working (exposure) period of 40 years (range: 28.8–144 mg) and the results were divided by body weight. An overview of the calculated data is given in Table 3.

Cancer risk assessment based on the epidemiological studies

From the study of Greene et al., the 10-year cumulative cancer risk per gram was calculated by using the median dose of 19.5 g among the total group and the corresponding 10-year cumulative cancer incidence of 5.4% [10]. A linear dose-response curve was constructed, using the 10-year cumulative cancer risk of 0.1% which was observed in the control group of patients without CP treatment. Finally, a 10-year cumulative cancer incidence of 0.27% per gram was calculated. A 10-year cumulative cancer incidence of 0.24% per gram was calculated by using the data of the highest dose group of 46.35 g and the corresponding 10-year cumulative cancer incidence of 11.1%.

The same procedure was followed for the results of the study by Baker et al. [4]. The 10-year cumulative cancer risk difference between CP-treated patients and control patients was calculated by linear extrapolation from the measured 10.8-year observation period to a 10-year period. The mean dose was 52.9 g, resulting in a 10-year cumulative cancer incidence of 0.21% per gram.

Results

Cancer risk assessment based on the animal study

Cancer risks were calculated for a health care worker of 70 kg body weight and a working (exposure) period of 40 years, 200 days a year. Within the range of the estimated mean daily CP uptake of 3.6–18 μg (total cumulative CP uptake over 40 years: 28.8–144 mg), the calculated lifetime risks of urinary bladder cancer in men and leukemias in men and women were nearly the same and ranged from 120 to 600 per million and from 95 to 475 per million, respectively (Table 3).

Cancer risk assessment based on epidemiological studies

Cancer risks were calculated by multiplication of the 10-year cumulative incidence per gram of CP in patients by the estimated mean total CP uptake in health care workers over 10 years, 200 days a year, based on the estimated mean daily uptake of 3.6–18 μg (total cumulative CP uptake over 10 years: 7.2–36 mg). No differences were found in the study on secondary

Table 3 Cancer risk calculations for health care workers obtained by linear extrapolation using incidence of tumors of the urinary bladder in male rats and of leukemias in male and female rats[a]

Parameter	Urinary bladder tumors	Leukemias
Rat		
Lowest dose with significant increase in tumors[b] (mg CP/kg body weight per day)	1.25	0.63
Tumor incidence[b] (%)	14.3	8.2
Median survival period (days)	646	889
Exposure period (days)	$(646 - 100) \times 5/7 = 390$	$(889 - 100) \times 5/7 = 564$
Total cumulated dose (mg CP/kg body weight)	$1.25 \times 390 = 487.5$	$0.63 \times 564 = 355$
Cancer risk per mg CP (kg body weight/mg CP)	$0.143/487.5 = 293 \times 10^{-6}$	$0.082/355 = 233 \times 10^{-6}$
Health care worker		
Lifetime cancer risk[c] (per million)	$1/70 \times 293 \times (28.8–144) = 120–600$	$1/70 \times 233 \times (28.8–144) = 95–475$

[a] From Schmähl and Habs [20]
[b] From Table 1
[c] 70 kg body weight; total cumulative CP uptake over 40 years: 28.8–144 mg

Table 4 Cancer risks for health care workers obtained from tumor incidence data of patients

Patients[a]		Exposed workers[b]	Reference
CP dose (g)	Cancer risk (per million)	Cancer risk (per million)	
Leukemias in women			
19.5[c]	54 000	20–100	Greene et al. [10]
46.35[d]	111 000	17–86	
0[e]	1 000		
Urinary bladder tumors and leukemias in men and women			
52.9[f]	112 000	15–76	Baker et al. [4]

[a] 10-year observation period
[b] 10-year exposure period (total cumulative CP uptake over 10 years: 7.2–36 mg)
[c] Median dose
[d] Highest dose group
[e] Control group without CP treatment
[f] Mean dose

tumors by Greene et al. between the results based on calculations with the median dose of the total group of 19.5 g and the highest dose group of 46.35 g (Table 4) [10]. In both cases cancer risk ranged from about 17 to 100 per million. A marginally lower cancer risk of 15 to 76 per million was obtained when primary tumor data from the study of Baker et al. were used (Table 4) [4].

Discussion

In the present study a cancer risk assessment of occupational exposure to CP was carried out following two approaches based on (1) data from an animal study and (2) data on primary and secondary tumors in CP-treated patients. During this operation several assumptions were made, and these are discussed below.

Tumor type

The same tumor types, namely urinary bladder tumors and leukemias, were found in the animals and in the patients. It is remarkable that urinary bladder tumors only appeared in male rats while leukemias were observed equally in male and female rats. Unfortunately, no information is available from the patient study of Baker et al. with respect to the sex-specific induction of urinary bladder tumors [4]. Consequently it is assumed that no sex differences were present. Because the study of Greene et al. only included women, it remains im-

possible to establish whether leukemias were induced in a sex-specific manner [10]. For extrapolation of the results of the animal study and patient studies this means that: (1) the animal study may only be used for risk assessment of urinary bladder tumors in men and of leukemias in men and women, (2) extrapolation from the patient study of Greene et al. is restricted to risk assessment of leukemias in women, and (3) it is assumed that the patient study of Baker et al. is suitable for the risk assessment of urinary bladder tumors and leukemias in men and women [4, 10].

Estimation of the daily uptake

For the estimation of the mean daily CP uptake, the excretion of unmetabolized CP in urine was investigated. In order to obtain accurate information about the daily CP excretion in urine, urine samples were collected from several persons over two to four periods of 4 successive days. In this way incidentally extremely high levels were averaged and overestimation was minimized. Nevertheless, a large interindividual difference in CP excretion was obtained, undoubtedly due to interindividual differences in uptake and/or biotransformation of CP. In order to compare the results of the different studies in a proper way, undetectable amounts of CP were set at zero. This results in an underestimation of the cancer risk. For the estimation of the uptake, we used results of studies in which relatively low amounts of CP were administered to rats and volunteers. Data of patients were not used because the amounts of CP administered were much higher than would be expected after occupational exposure.

The results of the animal study showed that a total of about 5% of a single CP dose of 1 mg/kg body weight was excreted in urine, all within 24 h, irrespective of the route of exposure (intratracheal, dermal, oral, or intravenous) [22]. Lowering of the dermally applied dose to 0.1 and 0.01 mg/kg body weight resulted in excretion percentages of 8.3% $\pm$ 2.1% and 5.1% $\pm$ 2.9%, respectively (mean $\pm$ SD, $n = 5$); these figures are not significantly different from one another (unpublished results). Therefore the excretion of unmetabolized CP is estimated to be about 5% of the administered dose. It is unclear why the percentage recovery of CP in urine in the volunteer study was only about 1% [12]. This may, of course, have been due to interspecies differences, but on the other hand it may also have been the result of incomplete absorption by the human skin. This latter possibility, which seems quite reasonable, would lead to an overestimation of both mean daily uptake and cancer risk if 1% excretion is taken as a starting point. Nevertheless, this is the only study in which volunteers have been treated with a relatively low CP dose. It should also be pointed out that the influence of chronic low-dose exposures by different exposure routes on the excretion percentage remains unknown.

Extrapolation

The data from the animal study showed a linear dose-response curve between daily CP dose and cancer risk. Consequently, linear extrapolation was used for cancer risk assessment. It should be noted that cancer risk is not primarily caused by the amount of CP absorbed but depends on the amount of phosphoramide mustard formed after biotransformation [31]. The formation of phosphoramide mustard results in the alkylation of target DNA and cancer risk is expected to correlate better with the amount of phosphoramide mustard able to bind to target tissue. On the basis of the linear dose-response relationship in the animal study between CP dose and cancer risk we assume that the amount of phosphoramide mustard increases linearly with the CP dose. Since biotransformation of CP in man and rat are similar, it is also reasonable to assume that in patients the amount of phosphoramide mustard will increase linearly with the dose [13, 31]. This explains our choice of the linear extrapolation when using the patient data.

Cancer risk

The results of the animal study showed a lifetime risk (70 years) of urinary bladder tumors in men and of leukemias in men and women of 95–600 per million after a period of CP exposure of 40 years, 200 days a year. Comparable cancer risks of 1.5–10 per million a year were estimated from the patient studies. It should be noted that in the animal study the number of lifetime cases was indicated while the cancer risk in patients was estimated on an observation period of 10 years. Since it is unclear how the dose-response curve will be after the 10-year observation period, it is not possible to show what the consequences will be for lifetime cancer risks. Therefore the calculated risks most probably are underestimates. It should also be noted that in the patient study of Greene et al. a possible predisposition of the patients under consideration may have resulted in higher cancer incidences upon treatment with genotoxic carcinogens [10]. It should be emphasized that in the study of Baker et al. the total cancer risk was assessed [4]. Not only urinary bladder tumors and leukemias were considered but also other types of cancer, especially skin cancer. This may partly explain the lower cancer risk calculated from the animal study as only urinary bladder tumors and leukemias could be taken into account here. Risks based on animal data should be calculated from the number of tumor-bearing animals, i.e., the sum of the number of animals having tumors at sites that show a statistically increased incidence as compared to controls. Unfortunately, the data of Schmähl and Habs do not allow such an approach, which might have resulted in higher estimated cancer risks [20].

Cancer risk and legislation

In the United States, Sweden, Germany, and the European Union, threshold limit values or comparable maximum exposure levels have been introduced for some (genotoxic) carcinogens in order to protect workers [3]. In The Netherlands it is proposed that, for workers, a cancer risk for each compound of 1 extra cancer case per million a year should be striven for ("target risk") and that no risk higher than 100 per million a year ("prohibitory risk") should be accepted [3]. From the animal and the patient study it appeared that the target risk is exceeded but that the risk is still below the prohibitory risk. Nevertheless, it should be noted that in some studies groups of workers have excreted higher amounts of CP than the mean daily CP excretion of 0.18 μg in the present study, consequently resulting in higher cancer risks (Table 2).

It should be emphasized that this risk assessment was based on exposure to one single antineoplastic agent while it is known that more antineoplastic agents are used for which no exposure data are available. However, it is reasonable to assume that exposure to all antineoplastic agents will occur in a similar manner because the drugs are mostly handled in a comparable way. In fact, this means that the cancer risk might be higher than assessed in the present study, supposing that no antagonistic interaction takes place. However, this is not of influence in the possible surpassing of target and prohibitory risk levels because these are based on single compounds.

In conclusion: The calculated cancer risk due to occupational exposure to CP was based on available dose-response data and on the indirect assessment of CP exposure by measuring CP excretion in urine. Although the presented cancer risk assessment due to exposure to CP has its limitations, the cancer risks calculated from CP exposure of health care workers indicate that these workers still have higher risks for cancer due to the handling of CP and/or other antineoplastic agents in spite of the protective measures that have been taken.

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