Table 1. *Distribution of* 115 *patients with lymphomas according to inclusion into clinical trials and selected characteristics: Italy,* 1995

Characteristics	Clinical trials		
	Included ($n=63$) No. (%)	Not included ($n=52$) No. (%)	Total ($n=115$) No. (%)
Age (years)			
≤ 64	50 (79)	35 (67)	85 (74)
≥ 65	13 (21)	17 (33)	30 (26)
Gender			
Male	32 (51)	22 (42)	54 (47)
Female	31 (49)	30 (58)	61 (53)
Type of lymphoma			
Non-Hodgkin's lymphoma	39 (62)	47 (90)	86 (75)
Hodgkin's disease	24 (38)	5 (10)	29 (25)
Stage			
I	9 (14)	18 (35)	27 (23)
II	16 (25)	12 (23)	28 (24)
III	18 (29)	8 (15)	26 (23)
IV	20 (32)	14 (27)	34 (30)
Grade—NHL*			
Low	10 (26)	20 (43)	30 (35)
Intermediate	22 (56)	18 (38)	40 (47)
High	6 (15)	3 (6)	9 (10)
Miscellaneous	1 (3)	6 (13)	7 (8)

*It includes only 86 patients with non-Hodgkin's lymphomas.

We took advantage of an ongoing study on the economic evaluation of extra costs attributable to phase II and phase III trials among patients with non-Hodgkin's lymphomas (NHL) and Hodgkin's disease (HD) to quantify the proportion of lymphoma patients who were actually enrolled into clinical trials at Aviano Cancer Centre, North east Italy, one of the six public National Cancer Institutes. Data regarding all newly diagnosed patients with NHL and HD, and discharged in the first study year (i.e. 1995), are herein reported.

Table 1 shows the characteristics of the 115 patients with malignant lymphomas under investigation, according to inclusion in clinical trials. Among these patients, 52 (45%) were not included in clinical trials and, therefore, underwent standard treatments. Exclusion from trials was significantly more frequent among patients with NHL (55%) than among those with HD (17%) ($\chi^2_1 = 10.79$, $P = 0.001$). Patients not included in trials tended to be older and to have more favourable stages of disease than those included, but these differences (Table 1) were not statistically significant. Patients with low-grade NHL or with miscellaneous histologies were less frequently included in clinical trials than patients with intermediate- or high-grade disease (Table 1) (χ^2_1 for trend $= 4.41$, $P = 0.04$).

As concerns individual's exclusion criteria from clinical trials conducted at Aviano Cancer Centre in 1995, 20 (39%) out of the 52 patients were not included in trials because of stage and 12 (23%) because of histology, since the concurrent trials were chiefly targeted to advanced diseases. 12 patients (23%) could not be enrolled because they lived too far away from the Institute, while 8 patients (15%) were excluded because of old age (i.e. more than 69 years). Of the 63 patients included in trials, 12 (19%) entered phase II and 51 (81%) phase III trials.

Although the present analysis was based on a small number of patients, and restricted to 1 year's activity, our findings are consistent with those reported by the Sheffield Lymphoma Group, where 55% of patients with malignant lymphomas were not entered into clinical trials [3]. The majority of those patients were excluded because of medical conditions (37%) or age (28%), with only 7% not enrolled due to the clinicians' decision [3].

Our results confirm that even in research-oriented clinical institutions, nearly half the patients with malignant lymphomas are not entered into clinical trials. In contrast, we have not documented exclusions attributable to the clinicians' decision, while old age represented, at our Centre, a less frequent exclusion criterion compared to the Sheffield Lymphoma Group, since a major effort to involve elderly patients in clinical trials has been made for some years [4].

Finally, our results point to a particular lack of clinical trials on well-differentiated lymphomas, for which traditional cytotoxic anticancer agents work less and new approaches are most needed [5].

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Human Transplacental Passage of the Retinoid Fenretinide (4HPR)

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WE INVESTIGATED whether 4HPR, a synthetic retinoid currently under investigation for the prevention of epithelial

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Table 1. *Concentration of 4HPR, 4MPR and retinol (ng/ml or ng/g of tissue) in human maternal plasma, placenta and embryo*

Patient	Age at conception (years)	4HPR treatment* Before conception (months)	After conception (days)	Interval from last drug intake (days)		4HPR	4MPR	Retinol (at baseline)†
1	42	20	19	53	Plasma	5	49	281 (464)
					Placenta	Traces	15	140
					Embryo	Traces	Traces	45
2	45	27	46	10	Plasma	26	87	323 (507)
					Placenta+Embryo‡	25	75	130

*The two patients, participating in a phase III trial on breast cancer prevention, were treated with 4HPR (200 mg/day) with a 3-day drug interruption at the end of each month. †Retinol plasma concentrations at baseline are reported in parentheses. ‡The embryo and a sample of placenta could not be isolated and identified. Traces = approximately 3 ng/g.

tumours and precancerous lesions [1], crosses the human placenta. Retinoids are potent human dismorphogens and, in spite of the low experimental teratogenicity [2] of 4HPR, its possible teratogenicity in humans is of concern in light of its long administration to the female participants of ongoing trials. According to the protocol of the breast cancer prevention trial [3], all patients of childbearing potential had to have a negative pregnancy test before starting therapy and to sign an informed consent about their willingness of avoiding pregnancy. In spite of this, 2 patients conceived 20 and 27 months, respectively (Table 1), after the beginning of 4HPR treatment. According to the estimated day of conception, they unintentionally kept taking 4HPR for 19 and 46 days, respectively and pregnancies were terminated 53 and 10 days after drug interruption. We obtained, with the informed consent of the 2 patients, the embryos and maternal blood samples at the time of pregnancy termination. Embryos could not be examined for malformations. Drug concentrations were measured by HPLC as previously described [4]. In the plasma, 4HPR could be detected in both patients (Table 1) and the concentrations of the metabolite *N*-(4-methoxyphenyl)retinamide (4MPR) were higher than those of the parent drug. In the placenta and the embryo of patient no. 1, who had interrupted drug treatment for almost 2 months, the concentrations of 4HPR were at the limit of detectability and the concentrations of 4MPR were lower than in plasma. In the other patient, who had taken the drug for a longer period and who had interrupted drug treatment for 10 days, the concentrations of 4HPR and 4MPR in the placenta and fetus were similar to those in the plasma. All-*trans*-retinoic acid (all-*trans*-RA), the most teratogenic retinoid in experimental systems, could not be detected in any sample (limit of detectability = 3 ng/ml or ng/g). 4HPR causes a reduction of retinol plasma levels [4] and this might be of concern for its teratogenicity since not only vitamin A excess but also vitamin A deficiency induce malformations in several species. In rats [2], 4HPR was only weakly teratogenic, and the levels of retinol in fetuses were diminished by 25–35% compared to controls. In both patients, the plasma concentrations of retinol were reduced compared with baseline values. Nothing can be said about the effects of 4HPR on the retinol concentrations of the placenta and the embryo, since no control value was available.

Our data show that 4HPR crosses the human placenta. In contrast to what happens with isotretinoin (13-*cis*-retinoic acid), a known human teratogen [5], 4HPR is not converted to all-*trans*-RA and it is not stored in the embryo, since several days after treatment interruption its concentration in embryo and placenta were lower than in plasma.

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