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TOXICITY, PHYSICAL FUNCTION AND EVERYDAY ACTIVITY REPORTED BY PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER IN A RANDOMIZED TRIAL (CHEMOTHERAPY VERSUS RADIOTHERAPY).

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Abstract

In a randomized trial, patients with inoperable non-small cell lung cancer with limited disease were randomly given either radiotherapy (42 Gy) or combination chemotherapy with cisplatin, 70 mg/m^2, and etoposide, 100 mg/m^2, given every third week with a maximum of 4 cycles. The patients were asked to fill in a questionnaire concerning psychosocial well-being, medical and treatment related symptoms, physical function and everyday activity. Of the chemotherapy patients 61% reported nausea 5 weeks after their last chemotherapy session and 44% had spells of vomiting. Only 14% of the radiotherapy patients had nausea and 5% vomited 14 weeks after start of treatment. Of the radiotherapy patients 64% experienced dysphagia compared to 8% of the chemotherapy patients 6 weeks after the start of treatment .

Key words: Lung neoplasms; non-small cell cancer, radiotherapy, chemotherapy, randomized trial, toxicity, quality of life.

In patients with inoperable limited non-small cell lung cancer (NSCLC) treated by combined chemotherapy and/or radiotherapy, a mean survival of 8–12 months has been reported (22, 36, 53). Treatment is often associated with side-effects such as nausea, vomiting, hair loss, dysphagia, and loss of appetite (6, 16, 32).

At the Norwegian Radium Hospital (NRH), the clinical toxicity, physical function and everyday activity in a number of patients were compared before, during and after combination chemotherapy or megavoltage radiotherapy in a randomized trial.

Material and Methods

Patients and treatment characteristics. Patients with inoperable NSCLC, limited disease, previously untreated, ≤70 years of age with a WHO performance grade ≤2 (57), were randomly assigned either to combination chemotherapy or to radiotherapy. The patients were given routine information about the common side-effects before the start of treatment. The combination chemotherapy consisted of cisplatin, 70 mg/m^2, and etoposide, 100 mg/m^2, given as an infusion on day 1. On days 2 and 3 etoposide, 200 mg/m^2, was given orally. The total hydration was 2500 ml with saline and 2000 ml with glucose on day 1, given over a period of 6–8 h. All the patients received 20 mg metoclopramide and 50 mg chlorpromazine before the start of chemotherapy and thereafter upon request.

With radiotherapy, a total of 42 Gy was given in 15 fractions over a period of 3 weeks, irradiating opposing anterior – posterior fields, including the tumor, hilus, and mediastinal lymph nodes. A shield was used when the posterior field was treated in order to reduce the spinal dose to ≤2.6 Gy per fraction. If metastases were present in the supraclavicular fossa, they were included into the field.

Design of the questionnaire. A questionnaire covering 4 areas viz. psychosocial well-being (quality of life), clinical toxicity (medical and treatment related symptoms), physical function, and everyday activities was given to each patient. The findings as regards medical and treatment related symptoms, physical function and everyday activity are presented here. The findings concerning the patient's psychosocial well-being is simultaneously published in this journal (24).

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A set of 10 questions (M1–M10, Part M) were designed to measure the disease and treatment related symptoms (Table 1). The scale was based on clinical experience and previously published reports (12, 35, 40, 49). The patients were asked to report the degree of symptoms before treatment on a 4-point scale with options ranging from 'never' to 'a great deal'.

The same 10 questions with yes/no answer alternatives were used during and after treatment. Information about the duration of the symptoms was also obtained. The evaluation of symptoms has been found to have a high degree of validity in a previous study with the exception of the item M6 ('sore, and red skin'). This question was included to evaluate its accuracy in the present study with multiple measurements over time.

Sets of questions on physical function (F1–F3) and everyday activity (A1–A4) were constructed, inspired by the EORTC lung cancer questionnaire (Table 2). These were designed as a Guttman scale (18), which is a scale constructed according to a set of questions with response choices representing a continuum of increasing levels of intensity, difficulty, and severity. Two requirements have to be met, unidimensionality and cumulativeness (38). In order to be unidimensional, the questions have to measure a single quality or dimension. It should be possible to average the questions by degree of difficulty or severity in order to be cumulative. This means that an individual who responds affirmatively to a question, indicating serious disability, should always respond affirmatively also to a question, indicating less disability, e.g. if the patient answers that he stays in bed, this implies that he is indoors most of the time.

Study design. The patients completed the questionnaire before treatment and one day after the first day of treatment in the hospital. Two weeks after the start of treatment the questionnaires were mailed to the chemotherapy patients, while the radiotherapy group completed the questionnaire at the hospital. After 6 weeks, the questionnaire was mailed to the radiotherapy patients while the chemotherapy patients answered the questionnaires at the hospital. All the patients were readmitted 14 weeks after the start of treatment for control purposes. Every second month for one year, the whole questionnaire was mailed to the patients (see ref. 24, Fig. 1, page 337 of this issue). The scale of clinical toxicity questions were included for the first 14 weeks.

Literature review. A Medline search was made for the years 1983, 1984, and 1985 to investigate the incidence of nausea and vomiting reported in cancer clinical trials. Three key words were utilized: neoplasm, non-small cell lung cancer, and chemotherapy, and 99 articles were found. Only articles in English with results based on combination chemotherapy were selected. Short communications were excluded because they reported toxicity to a very limited extent. The method of investigation and the reported incidence of nausea and vomiting were recorded.

Table 1

Clinical toxicity questionnaire (part M). The questionnaire was originally in Norwegian and was translated into English for publication

Did you have any of the following symptoms during the last fortnight?

		Never	Little	Quite a bit	Very much
M 1	Did you have nausea?	____	____	____	____
M 2	Did you vomit?	____	____	____	____
M 3	Did you have hair loss?	____	____	____	____
M 4	Did you have trouble swallowing?	____	____	____	____
M 5	Did you have sore throat?	____	____	____	____
M 6	Did you have sore and red skin?	____	____	____	____
M 7	Were you tired?	____	____	____	____
M 8	Did you lack appetite?	____	____	____	____
M 9	Did you have trouble sleeping?	____	____	____	____
M 10	Did you have pain?	____	____	____	____

Table 2

Physical function (part P) and everyday activity (part A) questionnaire. The questionnaire was originally in Norwegian and was translated into English for publication

		Yes	No
A 1	Do you have to stay indoors most of the day?	____	____
A 2	Are you in bed most of the time?	____	____
A 3	Do you have any trouble climbing one flight of stairs?	____	____
A 4	Do you need help to bath, dress or using the toilet?	____	____

Are you short of breath when you ...

		Not at all	Little	Quite a bit	Very much
F 1	Are at rest?	____	____	____	____
F 2	Walk?	____	____	____	____
F 3	Climb stairs?	____	____	____	____

Table 3

Baseline clinical toxicity scale (1–4)[a]

Variable	Radio-therapy (n=51)	Chemo-therapy (n=44)	p-value Student's t-test
Nausea	1.31	1.25	0.59
Vomiting	1.14	1.14	0.99
Hair loss	1.14	1.07	0.38
Dysphagia	1.10	1.11	0.83
Sore throat	1.26	1.27	0.85
Sore, red skin	1.02	1.05	0.49
Tiredness	1.82	1.71	0.47
Reduced appetite	1.55	1.75	0.21
Sleeping problems	1.86	1.65	0.22
Pain	1.71	1.41	0.05

[a] Mean values of the medical side-effect questions evaluated on a 4-point scale ranging from never (1) to very much (4).

Table 4

Clinical toxicity. Percentage of patients reporting symptoms

Variable	Treatment group	Time after start of treatment							
		2 days		2 weeks		6 weeks		14 weeks	
		%	p	%	p	%	p	%	p
Nausea	RT	13	<0.00001	43	0.001	37	0.0005	14	<0.00001
	CT	71		80		77		61	
Vomiting	RT	4	<0.00001	11	<0.00001	23	<0.007	5	<0.0005
	CT	68		69		54		44	
Hair loss	RT	2	1.0	44	<0.00001	7	<0.0001	8	<0.00001
	CT	2		64		90		63	
Dysphagia	RT	2	0.55	75	<0.00001	64	<0.00001	22	0.29
	CT	7		18		8		9	
Sore throat	RT	13	0.85	66	<0.00001	59	<0.00001	24	0.35
	CT	9		10		8		13	
Tiredness	RT	40	0.003	60	0.48	55	0.85	10	0.05
	CT	71		70		59		53	
Reduced appetite	RT	23	0.02	62	0.12	55	1.0	32	0.14
	CT	48		80		56		53	
Sleeping problems	RT	29	0.64	34	0.93	34	0.26	27	0.23
	CT	23		31		21		13	
Pain	RT	17	0.95	45	0.11	41	0.009	24	1.0
	CT	14		26		13		22	

RT = radiotherapy, CT = chemotherapy, p-values are based on χ^2-tests.

Other subjective side-effects, such as lack of appetite, sleeping problems, and pain were rarely reported and therefore impossible to review.

Statistical procedure. For Part M of the questionnaire, the mean scores for each treatment group were calculated before the start of treatment. Means were based on 5-point frequency measures. A 2-tailed Student's t-test (38) was used to evaluate statistical significance. The percentage of patients reporting symptoms during and after each treatment was calculated for each treatment modality separately. χ^2-tests (38) were used to assess the statistical significance of differences between the 2 treatment modalities. Yates' correction was used in the analysis.

In order to evaluate the scalability of the 2 sets of questions (physical function and everyday activity), the coefficients of reproducibility and scalability were calculated. The *coefficient of reproducibility* measures the extent to which a patient's pattern of response on separate items can be predicted from the scale. A general guideline for this coefficient is that it should be higher than 0.90 to be statistically significant. The *coefficient of scalability*, should be above 0.60 (38).

When constructing a Guttman scale, each item in the scale should have a single cutting point. In the physical function scale a distinction was made between 'not at all' on the one hand, and 'a little', 'quite a lot' and 'a great deal' on the other. For the everyday activity scale, only 2 response alternatives were presented, and so it was not necessary to choose a cutting point. In the statistical analysis 'no' or 'not at all' was given a value of 0 and 'yes', 'a little', 'quite a lot' and 'a great deal' a value of 1. The total was added up for each patient and the mean for each treatment group was calculated. The mean can thus vary between 0 and 3, with 0 as the best possible score. Two-tailed Student's t-tests were used to assess the statistical significance of group differences.

Results

Fifty-one patients (100%) in the radiotherapy group and 44 patients (100%) in the chemotherapy group completed the entire questionnaire before treatment. After 14 weeks, compliance had dropped to 37 patients (73%) in the radiotherapy group and 32 (73%) in the chemotherapy group.

Clinical toxicity. Baseline evaluation was made before the start of treatment when the patients had been informed about which treatment modality they were randomized to receive. Table 3 shows the baseline mean scores for each of the 2 treatment modalities. Sleeping disturbance, pain, tiredness, and lack of appetite were predominant symptoms (mean score 1.55 to 1.86), while the other symptoms occurred infrequently (1.02 to 1.31).

Despite randomization, the radiotherapy group reported significantly more pain than the chemotherapy group (p= 0.05) before the start of treatment.

In the following, the percentage of patients reporting each symptom is presented (Table 4). Nausea, vomiting and hair loss were predominant in the chemotherapy group, with statistically significant differences for all but one of the time points. Concerning dysphagia and sore throat there were no differences between the 2 treatment modalities after 2 days. At 2 weeks (during the last third of radiotherapy) and 6 weeks the radiotherapy patients reported more dysphagia and sore throat than the chemotherapy patients. A decrease of these symptoms was seen at 14 weeks for the radiotherapy group and at this time there were no differences between the 2 groups.

Patients receiving chemotherapy were significantly more tired and had less appetite after one day. However, there were no differences in these symptoms after 2 and 6 weeks. After 14 weeks, more chemotherapy patients than radiotherapy patients reported tiredness. The radiotherapy patients did not report a higher frequency of tiredness at any time. There were no differences between the groups regarding sleeping problems. However, the radiotherapy patients never reported better sleep than the patients who received chemotherapy. More radiotherapy patients had pain after 6 weeks as compared to those in the chemotherapy group. A relatively large proportion of patients receiving radiotherapy reported pain during the evaluation period than at the start of treatment; however, this decreased to 24% at 14 weeks.

Physical function and everyday activity. The physical function scale showed high reproducibility (>0.95) and scalability (>0.85) for all 4 evaluations. The everyday activity scale showed low scalability (<0.60). Closer analysis of the scale indicated that the question 'Do you have trouble climbing one flight of stairs?' had a low correlation with the rest of the items. This item was therefore excluded from the scale. A new scale was constructed with the 3 remaining items. It showed high reproducibility (>0.95) and scalability (>0.75).

Table 5 presents the above mentioned index. Chemotherapy patients reported significantly better physical performance before the start of treatment than the radiotherapy patients. (Lower scores indicate better physical function.) No group differences were seen and no temporal trend was noted. The highest score for both groups was seen at 6 and 14 weeks. A score of 2.0 indicates that the majority of the patients say that they are short of breath when they 'climb stairs' (F1) and 'walk' (F2).

For the everyday activity index (Table 6), there were no group differences and no temporal trends. A score of 2.0 indicates that most patients answered that they 'had to stay indoors most of the day' (A1) and they 'needed help to bath, dress or use the toilet' (A4).

Literature review. Table 7 shows a review of the incidence of nausea and vomiting reported in 34 articles, in patients undergoing combination chemotherapy for inoperable non-small cell lung cancer. In 81% of the publications, cisplatin was used as part of the combination chemotherapy. In 2 reports (6%), nausea and vomiting were not mentioned. Four articles (11%) reported the method applied, i.e. WHO toxicity scale and other scales. In the remaining 29 publications (82%) the method of measurement was not reported. In 14 articles (40%) measures of incidence of nausea and vomiting were approximated. ('All patients had nausea and most of the patients vomited, etc.') Fifteen (42%) reported the percentage or the number of patients with these symptoms. Only acute

Table 5

Physical function scale

Time of administration	Treatment	No.	Mean	SD	p-value
Before start of treatment	RT	51	1.61	0.90	0.02
	CT	44	1.16	0.99	
After 2 weeks	RT	43	1.67	0.81	0.23
	CT	37	1.43	0.96	
After 6 weeks	RT	42	1.76	1.0	0.88
	CT	37	1.73	0.90	
After 14 weeks	RT	35	1.66	0.84	0.67
	CT	31	1.74	0.82	
After 23 weeks	RT	28	1.46	0.96	0.09
	CT	28	1.43	0.74	
After 33 weeks	RT	27	1.26	0.94	0.41
	CT	20	1.59	1.0	
After 42 weeks	RT	18	1.44	0.86	0.43
	CT	19	1.21	0.91	
After 52 weeks	RT	15	1.27	1.27	0.42
	CT	14	1.50	1.50	

RT = Radiotherapy, CT = Chemotherapy.

Table 6

Everyday activity scale

Time of administration	Treatment	No.	Mean	SD	p-value
Before start of treatment	RT	50	2.16	0.42	0.47
	CT	44	2.23	0.48	
After 2 weeks	RT	46	2.04	0.52	0.95
	CT	39	2.05	0.65	
After 6 weeks	RT	44	2.05	0.53	0.55
	CT	39	2.13	0.70	
After 14 weeks	RT	36	2.28	0.74	0.80
	CT	30	2.23	0.68	
After 23 weeks	RT	31	2.29	0.64	0.27
	CT	29	2.10	0.67	
After 33 weeks	RT	28	2.07	0.81	0.40
	CT	20	2.25	0.64	
After 42 weeks	RT	19	2.42	0.61	1.0
	CT	19	2.42	0.51	
After 52 weeks	RT	15	2.13	0.92	0.77
	CT	14	2.21	0.58	

RT = Radiotherapy, CT = Chemotherapy.

Table 7

A review of reported acute nausea and vomiting in clinical trials. Non-small cell lung cancer treated with combination chemotherapy. Medline search 1983–85, in English

Assessment of method applied (n=3%)	No. of reports (ref. No.)	(%)	Percentage of patients with nausea and vomiting	
			Mean	Range
Not reported	2 (41, 54)	(6)	–	–
Approximation	14 (3, 4, 8, 13, 20, 28, 30, 33, 34, 42, 45, 47, 55, 56)	(40)	–	–
No. of patients with symptoms	14 (9–11, 19, 26, 29, 31, 37, 39, 44, 46, 48, 50, 52)	(42)	77	20–100
Other scales	3 (5, 14, 43)	(9)	41	11–70
WHO toxicity scale	1 (23)	(3)	(66% grade 1 and 2 31% grade 3 and 4)	

symptoms were reported. None of the articles reported side-effects in the follow-up period.

Discussion

Acute nausea and vomiting are commonly reported to occur in 70–80% of the patients receiving combination chemotherapy involving cisplatin (9, 37, 39, 46, 48, 52). However, when intensive antiemetics are given, such as high-dose metoclopramide and dexamethasone, the incidence of 'major' nausea and vomiting may be reduced (2, 15, 27). In the present study, 61% had nausea and 44% spells of vomiting 5 weeks after the last chemotherapy. Clinical experience indicates that these symptoms may be overreported. One possible explanation is that the presentation of the questionnaire may produce conditioned reflex nausea and/or vomiting. The present method may be invalid, i.e. too many patients may have reported iatrogenically provoked symptoms. However, it is also possible that the symptoms are underreported in the oncological literature in lung cancer. According to the literature review, only 3% of the studies used the WHO toxicity criterion. Nausea and vomiting were not reported in the follow-up period (subacute toxicity) in any of the studies (Table 7).

Nausea and vomiting were studied in patients with breast cancer treated with adjuvant chemotherapy (CMF). One month after the last cycle of chemotherapy, 59% experienced conditioned reflex nausea and 35% conditioned reflex vomiting. The corresponding figures 5 months later were 37 and 7% respectively (21). Further studies should be made on the incidence of subacute and late nausea and vomiting in patients treated with combination chemotherapy.

Radiotherapy related side-effects, 'dysphagia' and 'sore throat' occurred later in the treatment period, and the duration was shorter than that of the side-effects of chemotherapy. At 2 weeks (the last third of the radiotherapy course), 75% of the patients reported dysphagia. This dropped to 64% after 6 weeks, and 22% at 14 weeks, and the group difference was not statistically significant at the last evaluation. Oesophagitis is known to be one of the most pronounced radiotherapy related side-effects for lung cancer patients (1, 17). However, it is rarely dose-limiting or a cause of serious late complications (6). In most reports, 40–100% of the patients experienced this particular symptom (7, 51). The duration of the symptom is rarely reported. In an article by Umsawasdi et al. (51), however, the median duration of oesophagitis during a combined treatment of chemotherapy and radiotherapy for small cell lung cancer was 3 weeks, which agrees with the present results. Of our radiotherapy patients 43% experienced nausea and 11% vomited during treatment (at 2 weeks). The incidence of these symptoms is rarely reported in clinical trials for patients treated with chest irradiation.

The clinical toxicity part of the questionnaire consisted of 10 questions. One of the questions dealing with subacute radiotherapy side-effects, 'sore, red skin' showed low validity in a previous study (25). In the present study, this specific question did not differentiate between the 2 treatment modalities. The question was meant to describe the acute local radiotherapy side-effects on the skin within the radiotherapy field. Thus, the present study says nothing about chemotherapy related skin problems or radiotherapy dermatitis. However, one would not expect any major skin-related side-effects from the radiotherapy. The question was excluded in further analyses.

The physical function and everyday activity index did not differentiate between the 2 treatment modalities. Response to treatment may be expected to improve a patient's physical function (36). In the present study, the

overall response rate was 25% (complete remission = 3%) for the radiotherapy group and 15% (complete remission = 1%) in the chemotherapy group, with a median survival of 10 months in both groups (22). With such a low complete response rate one would not expect any improvement or group difference with regard to physical function or everyday activity.

Subacute side-effects, such as chemotherapy related nausea and vomiting are not systematically measured in most studies. A rational approach to this question might be to use the WHO grading system for physicians' assessment of acute toxicity and furthermore to use questionnaires administered to the patients in the follow-up period. Questionnaires including both incidence and intensity measures seem appropriate.

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