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ERCC1, toxicity and quality of life in advanced NSCLC patients randomized in a large multicentre phase III trial

Adam Vilmar [a,*], *Eric Santoni-Rugiu* [b], *Jens Benn Sørensen* [a]

[a] *Department of Oncology 5073, Finsen Centre, National University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark*
[b] *Department of Pathology 5442, Diagnostic Center, National University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark*

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ABSTRACT

Aim: Excision repair cross complementation group 1 (ERCC1) is a promising biomarker in advanced non-small cell lung cancer (NSCLC). However, current evidence regarding the impact of ERCC1 on toxicity and quality of life (QOL) is limited.

Patients and methods: Four hundred and forty three patients with advanced NSCLC were enroled in a phase III trial and randomized to triplet chemotherapy or standard doublet regimen. Immunohistochemical evaluation for ERCC1-status was mainly performed on bioptic material. Toxicity and patient-reported QOL were correlated to ERCC1-status.

Results: We observed a significantly improved outcome in patients with ERCC1-negative (ERCC1-neg) tumours and demonstrated interaction between ERCC1-status and adenocarcinomas. Numerically more toxicity was observed in the entire population of ERCC1-neg tumours and reached significance in patients with adenocarcinomas regarding leukopenia ($P = 0.015$), nausea/vomiting ($P = 0.040$) and neurotoxicity ($P = 0.037$). Mean change in QOL in the entire population was −13.33 (ERCC1-neg; $P = 0.001$) and −2.25 (ERCC1-positive (ERCC1-pos): $P = 0.607$) and −14.86 (ERCC1-neg; $P = 0.006$) and 0 (ERCC1-pos) in patients with adenocarcinomas.

Conclusions: Patient-reported QOL deteriorated significantly among survival-favourable ERCC1-neg patients possibly due to increased toxicity especially in patients with adenocarcinomas. Our novel findings emphasise strict demands for careful patient selection, proper methodology and prospective validation of ERCC1 to prove a true survival benefit before clinical implementation.

1. Introduction

Translational research has provided unique knowledge in molecular cancer biology and thereby paving the way for new treatment options. Customising anti-cancer treatment by the use of biomarkers has improved outcome in a variety of malignant diseases beginning with hormone receptor status in breast cancer predicting sensitivity to anti-oestrogen therapy. During the same period Imatinib was approved for chronic myelogenous leukaemia (CML) characterised by the fusion gene *Bcr*-ABL. In recent years several other similar discoveries have emerged: e.g. the KRAS-mutation predicting resistance to Cetuximab in Colorectal Cancer (CRC).

Lung cancer has killed around 160.000 people in 2009 in the United States (US) alone (http://www.cancer.gov/cancertopics/types/lung) and is the leading cancer-related cause of death in the western world. Non-small cell lung cancer (NSCLC) accounts for the majority of the patients (80%) and is a relatively chemotherapy-resistant disease with response rates (RR) of 25–30% and median overall survival (OS) of

* *Corresponding author:* Tel.: +45 26808851; fax: +45 35456966.
E-mail address: adamvilmar@hotmail.com (A. Vilmar).
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10–12 months in patients with advanced disease (70%).[1] The dismal prognosis has warranted intensive translational research leading to the discovery of biomarkers with the potential to identify patient subgroups and improve outcome: Patients with mutations in the EGFR-gene are likely to benefit from Erlotinib,[2] histopathology and possibly low thymidylate synthase (TS)-levels may increase response to Pemetrexed[3] and the excision cross complementation group 1 (ERCC1) predicts sensitivity to Cisplatin.[4]

ERCC1 plays a key role in nucleotide excision repair (NER) pathway. NER repairs DNA-adducts and other DNA helix-distorting lesions including those associated with Cisplatin.[5] ERCC1 works together with its XP group F (XPF) partner by a 'cut and paste mechanism' where it nicks the damaged DNA strand at the 5′ site of the helix-distorting Cisplatin lesion[6] as well as by being involved in homologous repair of interstrand crosslinks.[7] Low expression of the ERCC1-gene (ERCC1-neg) may predict increased sensitivity to platinum-based chemotherapy possibly due to saturation of the enzyme complex, which is supported by a number of studies.[4,8–11]

However, only few studies[4,12,13] have explored the correlation between ERCC1-status and toxicity in advanced NSCLC and reported different results. Toxicity is an important issue if the biomarker is to be clinically applied. The increased effect of Cisplatin-based chemotherapy regimens in ERCC1-neg patients could potentially increase the toxicity and deteriorate quality of life (QOL). To our knowledge no research groups have explored the impact of ERCC1-status on QOL. In ovarian and gastro-intestinal (GI) cancer ERCC1 also appears to be a promising predictive marker and the impact of different ERCC1 single nucleotide polymorphisms (SNP) has been correlated with toxicity but with conflicting results.[14–17]

Taken together, the impact of ERCC1-status on toxicity is far from elucidated and dominated by heterogenous studies, using different methodologies and reporting varying conclusions. The objective of this study was to explore the correlation between immunohistochemically evaluated ERCC1-status, toxicity and QOL in a large homogeneous population of advanced NSCLC patients randomized in a chemotherapy trial.[18] Our group has previously shown an interaction between ERCC1-neg status and adenocarcinomas yielding a favourable Hazard Ratio (HR) in predicting Cisplatin sensitivity in advanced NSCLC patients.[19] Accordingly, we explored the toxicity profile and QOL in this subgroup of patients.

2. Materials and methods

2.1. Patients and treatment

A total of 443 chemotherapy-naive patients aged 18–75 years with histologically verified inoperable NSCLC, performance status 0–2 and normal organ function where included in the study (LU2007) and randomized to regimen A (Paclitaxel 180 mg/m^2 and cisplatin 100 mg/m^2 day 1 with Gemcitabine 1000 mg/m^2 day 1 and 8 every 3 weeks) or regimen B (Cisplatin 100 mg/m^2 day 1 every 3 weeks and weekly intravenously (i.v.) Vinorelbine for a maximum of 6 cycles) to examine for superiority in the intensive regimen. Antiemetic therapy was administered according to national guidelines prior, during and after treatment. Patients with brain metastasis were excluded. Totally 428 patients were needed to detect a 30% median survival increase with 80% power and two-sided type 1-error of 5%. Two hundred and sixty four of these patients had sufficient histological material to be included the retrospective ERCC1 tumour-marker study that was planned during the course of LU2007. Patients gave informed written consent.

The ERCC1 tumour-marker study and LU2007 were approved by The Danish National Committee on Biomedical Research Ethics and the Danish Data Protection Agency.

Characteristics are summarised in Table 1. Six patients with significant tumour shrinkage also received additional radiotherapy with curative intent following chemotherapy and one patient had surgery.

Patients were enroled in LU2007 from December 2000 until June 2007 and were censored as of December 2008. Clinical end-points in the ERCC1 tumour-marker study were RR (according to RECIST-criteria), Progression Free Survival (PFS) and OS. All toxicity variables were graded according to the National Cancer Institute Common Toxicity Criteria (CTC) (Version 2.0). Toxicity evaluation was performed at day 1 of every cycle until the end of treatment. The following variables were recorded: leukocytopenia, thrombocytopenia, nausea/vomiting, nephrotoxicity, neurotoxicity, worst other toxicity (e.g.: fatigue, alopecia, myalgia, etc.), number of febrile episodes and number of bleeding episodes.

2.2. QOL evaluation

QOL was assessed with the European Organization for the Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaire (QLQ-C30) and with the lung cancer questionnaire module QLQ-LC13 that is a trial-specific symptom checklist. Both questionnaires have been validated,[20,21] are widely used and were completed by the patients at baseline (before random assignment) and before each chemotherapy cycle. Only fully completed questionnaires were included. These were compared between baseline and before cycles 3, 4, 5 or 6 depending of availability as the number on completed questionnaires was limited.

2.3. Tissue samples

Archival paraffin blocks containing formalin-fixed NSCLC tissue from the 443 patients enroled in LU2007 were mainly obtained from the Departments of Pathology at the University Hospitals of Copenhagen, Odense and Aalborg. Two hundred and sixty four patients (59.5%) had sufficient biopsy material for ERCC1 evaluation. The histological samples consisted of 38 surgical resections, 195 biopsies (117 endoscopical, 57 mediastinoscopical and 21 transthoracic biopsies), and 31 miscellaneous (local biopsies from metastatic lesions including 8 clot-preparations of cytological specimens (pleural/pericardial effusions, fine needle aspirations)). Tissue samples were obtained from the primary lesion in 158 patients, from pulmonal/bronchial/mediastinal lymph nodes in 22 patients and from distant metastatic lesions in 36 patients. The remaining 48 patients had combinations of the three categories.

Table 1 – Characteristics of the patients in the ERCC1 tumour-marker study.

		No. of patients						
		ERCC1-negative		ERCC1-positive		Total		P-value
		(*n* = 139)	%	(*n* = 125)	%	(*n* = 264)	%	
Treatment	Regimen A	73	52.5	68	54.4	141	53.4	0.76
	Regimen B	66	47.5	57	45.6	123	46.6	
Gender	Male	71	51.1	89	71.2	160	60.6	0.01
	Female	68	48.9	36	28.8	104	39.4	
Age	Median	61.3		63		62.3		0.22
	Range	61.3–74.8		40.1–78.4		38.8–78.4		
LDH-levels (units/litre)	Median	312		328		321		0.56
	Range	139–4030		94–1684		94–4030		
Leucocyte count (×109/litre)	Median	8.9		9.9		9.4		0.06
	Range	4.7–31		3.3–40.0		3.3–40.0		
Performance status (WHO)	PS = 0	49	35.3	43	34.7	92	35	0.39
	PS = 1	80	57.6	66	53.2	146	55.5	
	PS = 2	10	7.2	15	12.1	25	9.5	
Histological subtype (WHO)	Adenocarcinoma	87	62.6	35	28.0	122	46.2	0.00
	Squamous cell carcinoma	19	13.7	56	44.8	75	28.4	
	Large cell carcinoma	5	3.6	4	3.2	9	3.4	
	NOS	28	20.1	29	23.2	57	21.6	
	Adenosquamous carcinoma	0	0	1	0.8	1	0.4	
Stage	IIIA/N2 (inoperable)	2	1.4	4	3.2	6	2.3	0.37
	IIIA/T3 (inoperable)	5	3.6	6	4.8	11	4.2	
	IIIB (dry)	30	21.6	34	27.2	64	24.2	
	IIIB (wet)	12	8.6	15	12.0	27	10.2	
	IV	90	64.7	66	52.8	156	59.1	

Abbreviations: ERCC1: Excision repair cross complementation group 1. LDH: Lactate dehydrogenase. PS: Performance status. NOS: Not otherwise specified: the histological subtype of NSCLC could not be classified on the basis of the available bioptic material.

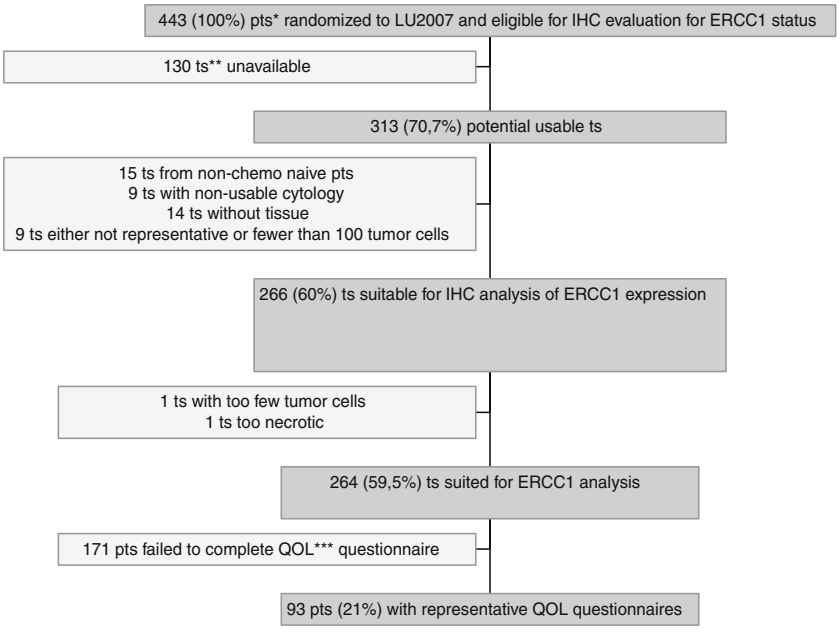

Fig. 1 – Flow chart of the patients' tissue samples through the excision repair cross complementation group 1 (ERCC1) tumour-marker study. *Patients. **Tissue samples. ***Quality of life.

2.4. *Immunohistochemical preparation of tissue samples*

Four micrometre-thick formalin-fixed paraffin embedded (FFPE) sections were cut and mounted on coated slide glass. From each tissue specimen, sections stained with haematoxylin–eosin were histologically evaluated for verification of diagnosis and eligibility for IHC analysis (Fig. 1 for more detailed information).

For ERCC1 immunostainings, FFPE tissue sections were deparaffinized and incubated in Tris/EGTA (TEG) buffer (pH 9.0) for 20 min at 97 °C for antigen retrieval using a DAKO Pt. link machine according to the manufacturer's instructions.

The tissue sections were then processed with the Envision Flex + kit (DAKO K 8002, DAKO, Denmark) blocking endogenous peroxidase activity for 5 min (min) and then incubating for 20 min at RT with the mouse monoclonal antibody ERCC1 Ab-2 (Clone 8F1; Thermo Fisher Scientific, Fremont, CA, USA) (diluted 1:200) against full-length human ERCC1. The reaction was visualised by incubation with Envision Linker (Mouse) for 15 min followed by Envision Flex + horseradish peroxidase (HRP) for 20 min and finally diaminobenzidine (DAB) for 10 min. The sections were counterstained with Mayer's haematoxylin for 1 min.

2.5. Immunohistochemical evaluation for ERCC1-status

ERCC1 nuclear expression was analysed as previously described.[10] Briefly, two observers (A.V., E.S.-R.) blinded to the clinical data independently evaluated ERCC1 immunostaining of the eligible tissue samples under a light microscope at a magnification of 400×. A semi quantitative *H*-score for each tissue sample was calculated multiplying the staining intensity of tumour cells (0: no expression, 1: weak expression, 2: moderate expression, 3: strong expression) by a proportion score based on the percentage of positive tumour nuclei (0 if 0%, 0.1 if 1–9%, 0.5 if 10–49%, and 1.0 if 50% or more). Endothelial cells in normal lymphatic tissue from lymph nodes and tonsils were used as positive control (corresponding to ERCC1 nuclear intensity of 2) as previously described.[10] Omission and substitution of ERCC1 Ab-2 with unspecific immunoglobulin were used as negative control. The proportion score was determined by counting at least 100 tumour cells per sample. In the event of discordance between the observers, the tissue section was re-evaluated to reach consensus.

The cut-off point was chosen *a priori* as the median value of all the *H*-scores to separate ERCC1-positive (*H*-score > median) tumours from ERCC1-negative (*H*-score ⩽ median) ones. The highest ERCC1 value was used when more than one tissue sample per chemotherapy-naive patient was available.

2.6. Statistical analyses

All statistical analyses were performed with the use of SPSS-software (SPSS version 15.0). The EORTC QLQ-C30 and LC13 were scored according to the EORTC guidelines.[22] Higher scores indicated better functioning in functional domains while higher scores in the symptom scales indicated deterioration. A change in score of ⩾10 points from baseline was defined as clinically significant.[22] Associations between categorial variables were compared by Chi-square test and Fisher's exact test. Odds ratios (OR) and 95% confidence intervals (CI) were reported on the basis of binary logistic regression analyses. To compare means the Student's *t*-test for individual or paired samples was used. *P*-values below 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the population

A total of 443 patients were randomized in the chemotherapy trial (LU2007) without statistical significant survival difference between the triplet regimen and the standard doublet regimen. Two hundred and sixty four patients (59.5%) of the 443 patients originally randomized to the two treatment arms could be immunohistochemically evaluated for ERCC1-status. The remaining 40.5% of patients could not be evaluated for ERCC1 due to unavailable tissue samples, no tumour tissue left, etc. (Fig. 1).

No difference in ERCC1-status was observed between the two treatment arms. Overall, there were slightly more males (60%) and in the female population 68 patients (65%) were ERCC1-neg. The majority of the patients (90%) had PS 1 or 2. Histological tissue samples mainly consisted of 122 (46.2%) adenocarcinomas, 87 (62.6%) of these being ERCC1-neg, and 75 (28.4%) squamous cell carcinomas, 56 (44.8%) of these being ERCC1-positive (ERCC1-pos). The median age was 62.4 years and the majority of patients (79.5%) received their treatment in Copenhagen (Table 1).

One hundred and four patients (53.6%) and 90 patients (46.4%) in regime A and regime B completed and returned the QLQ-C30 and LC13, respectively. The mean number of completed treatment cycles on questionnaire turn-in were 3 (range: 2–5). 93 patients (47.9%) had representative questionnaires for evaluation in the tumour-marker study. Fifty-five patients (59.8%) with ERCC1-neg tumours and 38 patients (40.2%) with ERCC1-pos tumours. The mean number of chemotherapy cycles completed on questionnaire turn-in was 3 in patients with ERCC1-neg tumours and 4 in patients with ERCC1-pos tumours.

3.2. Immunohistochemical evaluation for ERCC1-status

A *H*-score median value of 1 separated the population into 125 (47.3%) ERCC1-pos patients (*H*-score > 1) and 139 (52.7%) ERCC1-neg patients (*H*-score ⩽ 1). Considerable variation of the intratumoural immunostaining-intensity and frequency of positive nuclei was observed.

3.3. ERCC1-status and toxicity

Among the overall toxicity variables the leukopenia CTC Grades 2 and 3 were 33.1% and 34.5% (ERCC1-neg) versus (vs) 27.2% and 29.6% (ERCC1-pos), respectively ($P = 0.435$). leukopenia. The fraction of patients suffering from nausea/vomiting CTC Grade 2 were 36.7% (ERCC1-neg) versus 25.6% (ERCC1-pos), respectively ($P = 0.128$) (Table 2). The corresponding OR was 0.78 ($P = 0.047$, 95%CI, 0.61–0.99). No differences were observed between the two groups or their OR when the toxicity variables were divided into CTC grade 0–3 versus 4 or 0–2 versus 3–4 (Table 3).

In patients with ERCC1-neg adenocarcinomas ($n = 87$) the frequencies of leukopenia CTC Grades 2 and 3 were 31% and 41.4% versus 20% and 25.7% in patients with ERCC1-pos tumours ($n = 35$), respectively ($P = 0.015$). Frequencies of throm-

Table 2 – Common Toxicity Criteria (CTC) grades 0–4 (including 5 if recorded) and number of bleeding- and febrile leukopenia episodes among patients in the ERCC1 tumour-marker study.

		No. of patients				
		ERCC1-negative		ERCC1-positive		*P*-value
		n = 139	%	*n* = 125	%	
Leukocytopenia	NA	2	1.4	6	4.8	0.435
	0	17	12.2	19	15.2	
	1	9	6.5	9	7.2	
	2	46	33.1	34	27.2	
	3	48	34.5	37	29.6	
	4	17	12.2	20	16.0	
Thrombocytopenia	NA	2	1.4	6	4.8	0.226
	0	78	56.1	67	53.6	
	1	21	15.1	11	8.8	
	2	10	7.2	16	12.8	
	3	16	11.5	13	10.4	
	4	12	8.6	12	9.6	
Nausea/vomiting	NA	2	1.4	8	6.4	0.128
	0	20	14.4	25	20.0	
	1	39	28.1	39	31.2	
	2	51	36.7	32	25.6	
	3	26	18.7	20	16.0	
	4	1	.7	1	.8	
Nephrotoxicity	NA	2	1.4	8	6.4	0.303
	0	68	48.9	59	47.2	
	1	34	24.5	30	24.0	
	2	24	17.3	21	16.8	
	3	11	7.9	7	5.6	
	4	0	0	0	0	
Neurotoxicity	NA	2	1.4	9	7.2	0.285
	0	56	40.3	50	40.0	
	1	48	34.5	39	31.2	
	2	21	15.1	17	13.6	
	3	11	7.9	8	6.4	
	4	1	0.7	2	1.6	
Worst other toxicity	NA	2	1.4	6	4.8	0.548
	0	7	5.0	6	4.8	
	1	34	24.5	23	18.4	
	2	57	41.0	53	42.4	
	3	32	23.0	31	24.8	
	4	7	5.0	5	4.0	
	5	0	0	1	0.8	
No. of febrile leukopenia episodes	NA	4	2.9	7	5.6	0.315
	0	115	82.7	98	78.4	
	1	14	10.1	17	13.6	
	2	6	4.3	2	1.6	
	3	0	0	1	0.8	
No. of bleeding episodes	NA	4	2.9	7	5.6	0.594
	0	121	87.1	109	87.2	
	2	13	9.4	8	6.4	
	2	1	0.7	1	0.8	
	3	0	0	0	0	

bocytopenia CTC Grades 3 and 4 were 11.5% and 6.9% versus 5.7% and 2.9%, respectively ($P = 0.072$). In patients with ERCC1-neg tumours the frequencies of nausea/vomiting, nephrotoxicity and neurotoxicity CTC Grade 2 were 39.1%, 16.1% and 17.2% versus 31.4%, 8,6% and 8.6% in patients with ERCC1-pos tumours, respectively ($P = 0.040$, 0.074 and 0.037) (Table 4). No differences were observed between the two groups or their OR when the toxicity variables were divided into CTC 0–3 versus 4 or 0–2 versus 3–4.

3.4. *ERCC1-status and QOL*

The mean change in QOL from baseline was –13.33 points (CI: –5.60 to –21.06, $P = 0.001$) in patients with ERCC1-neg tumours

Table 3 – Common Toxicity Criteria (CTC) grades 0–2 versus 3–4 among patients in the ERCC1 tumour-marker study.

		No. of patients				
		ERCC1-negative		ERCC1-positive		*P*-value
		n = 139	%	*n* = 125	%	
Leukopenia	0–2	72	52.6	62	52.1	0.942
	3–4	65	47.4	57	47.9	
Thrombocytopenia	0–2	109	79.6	94	79.0	0.911
	3–4	28	20.4	25	21.0	
Nausea/vomiting	0–2	110	80.3	96	82.1	0.721
	3–4	27	19.7	21	17.9	
Nephrotoxicity	0–2	126	92.0	110	94.0	0.526
	3–4	11	8.0	7	6.0	
Neurotoxicity	0–2	125	91.2	106	91.4	0.969
	3–4	12	8.8	10	8.6	
Worst other toxicity	0–2	98	71.5	82	68.9	0.647
	3–4	39	28.5	37	31.1	
No. of febrile leucopenia episodes	0–2	129	95.6	115	97.5	0.509
	3–4	6	4.4	3	2.5	
No. of bleeding episodes	0–2	134	99.3	117	99.2	1.0
	3–4	1	0.7	1	.8	

(Fig. 2). In the subgroup of patients with adenocarcinomas ($n = 46$) and ERCC1-neg tumours ($n = 37$) the mean change in QOL from baseline was −14.86 points (CI: −4.89 to −25.24, $P = 0.006$) (Fig. 3). There was no difference in fractionated QOL (unchanged, worse, improved) according to the ERCC1-status.

4. Discussion

ERCC1 has previously been shown to be a promising biomarker in NSCLC[4,10] and in other malignancies such as ovarian cancer[23,24] and GI-cancer.[25,26] However, the evidence regarding the role of ERCC1-status in toxicity and QOL is sparse and heterogenous, especially in patients with advanced NSCLC. A tolerable toxicity profile is of great importance if clinicians are to customise chemotherapy treatment based on ERCC1-status and the survival benefit should be weighted against a possible deterioration of QOL.

The objective of this study was to explore the correlation between immunohistochemically evaluated ERCC1-status, toxicity and QOL in a homogeneous, randomized, multicentre population diagnosed with advanced NSCLC.

Our baseline population consisted of 443 patients who were randomized to Cisplatin-based triplet chemotherapy or a standard doublet chemotherapy. Two hundred and sixty four patients had representative tissue samples available for immunohistochemical evaluation. We demonstrated a statistically significant improved outcome (PFS and OS) in ERCC1-neg patients.[19]

In the present study we observed a general tendency toward increased toxicity among ERCC1-neg patients although it did not reach statistical significance and an OR of 0.78 for nausea/vomiting in patients with ERCC1-pos tumours.

We have previously demonstrated an interaction between ERCC1-status and histopathology.[19] Therefore, we also explored the toxicity in patients with adenocarcinomas. Statistically significant more toxicity was demonstrated in patients with ERCC1-neg adenocarcinomas regarding leukocytopenia, nausea/vomiting, nephrotoxicity and neurotoxicity.

To our knowledge we are the first research group to explore QOL in a ERCC1-study. Although the relatively low number of questionnaires completed ($n = 93$) indicates cautious interpretation, we observed a tendency similar to that of toxicity: a statistically and clinically significant deterioration of QOL among patients with ERCC1-neg tumours and especially in patients with ERCC1-neg adenocarcinomas.

Taken together, our results indicate that the survival-favourable ERCC1-neg patients suffer more toxicity, although it does not appear to translate into the clinically significant CTC grades 3 and 4 including the important toxicity variable leukopenia. However, the deterioration of QOL in this subgroup emphasise the demands for careful patient selection, proper methodology and prospective validation to prove a true survival benefit ahead of clinical implementation.

The limitations of our study are the unavailable tissue samples in 40% of the patients, the fact that ERCC1 tumour-marker study was not preplanned in the randomized trial (no control group, possible confounders, etc.) and that the patients were treated with two different chemotherapy regimens. Furthermore, the limited number of completed QOL questionnaires warrants cautious interpretation. In addition, the baseline questionnaire was compared to the available questionnaire during treatment that varied in number of cycles completed (2–5). This was necessary in order to obtain a representative amount of evaluable patients. As shown in Table 1 there is a imbalance in the frequency of adenocarcinomas' (predominantly ERCC1-neg) and squamous cell carcinomas' (predominantly ERCC1-pos) ERCC1-status. These histopathological tendencies, however, are in line with

Table 4 – Common Toxicity Critieria (CTC) grades 0–4 (including 5 if recorded) and number of bleeding- and febrile leukopenia episodes among patients in the ERCC1 tumour-marker study with adenocarcinomas.

		No. of patients				
		ERCC1-negative		ERCC1-positive		*P*-value
		n = 87	%	*n* = 35	%	
Leukocytopenia	NA	0	0	3	8.6	0.015
	0	8	9.2	8	22.9	
	1	7	8.0	3	8.6	
	2	27	31.0	7	20.0	
	3	36	41.4	9	25.7	
	4	9	10.3	5	14.3	
Thrombocytopenia	NA	0	0	3	8.6	0.072
	0	50	57.5	19	54.3	
	1	12	13.8	4	11.4	
	2	9	10.3	6	17.1	
	3	10	11.5	2	5.7	
	4	6	6.9	1	2.9	
Nausea/vomiting	NA	0	0	3	8.6	0.040
	0	13	14.9	7	20.0	
	1	23	26.4	6	17.1	
	2	34	39.1	11	31.4	
	3	17	19.5	7	20.0	
	4	0	0	1	2.9	
Nephrotoxicity	NA	0	0	3	8.6	0.074
	0	42	48.3	16	45.7	
	1	24	27.6	10	28.6	
	2	14	16.1	3	8.6	
	3	7	8.0	3	8.6	
	4	0	0	0	0	
Neurotoxicity	NA	0	0	3	8.6	0.037
	0	35	40.2	12	34.3	
	1	30	34.5	14	40.0	
	2	15	17.2	3	8.6	
	3	7	8.0	2	5.7	
	4	0	0	1	2.9	
Worst other toxicity	NA	0	0	2	5.7	0.458
	0	6	6.9	2	5.7	
	1	18	20.7	6	17.1	
	2	40	46.0	14	40.0	
	3	19	21.8	9	25.7	
	4	4	4.6	1	2.9	
	5	0	0	1	2.9	
No. of febrile leukopenia episodes	NA	1	1.1	3	8.6	0.315
	0	73	83.9	29	82.9	
	1	9	10.3	3	8.6	
	2	4	4.6	0	0	
	3	0	0	0	0	
No. of bleeding episodes	NA	1	1.1	3	8.6	0.594
	0	76	87.4	31	88.6	
	1	9	10.3	1	2.9	
	2	1	1.1	0	0	
	3	0	0	0	0	

previously published results.[9,10] Other research groups have explored the correlation between ERCC1-status and chemotherapy toxicity in advanced NSCLC but with different methodologies. Single nucleotides polymorphisms (SNP) are variations from the wild-type (WT) alleles and Isla and colleagues[13] found a statistically significant survival benefit in patients with the ERCC1-118 C/C (WT) allele combination but no difference in toxicity. The same result was shown by Tibaldi and co-workers.[27] However, no survival advantage among different SNP was demonstrated. In contrast Suk

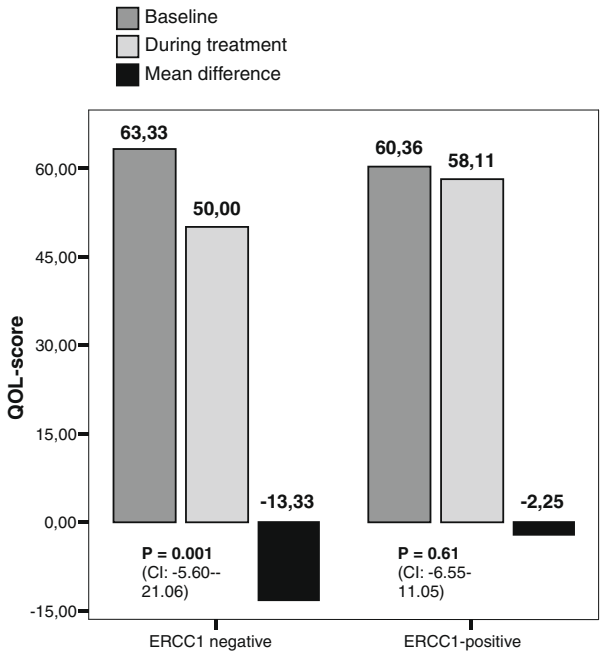

Fig. 2 – Alteration in selfreported quality of life (QOL) among 93 patients with advanced non-small cell lung cancer (NSCLC) stratified according to the excision repair cross complementation group 1 (ERCC1) tumour-marker status.

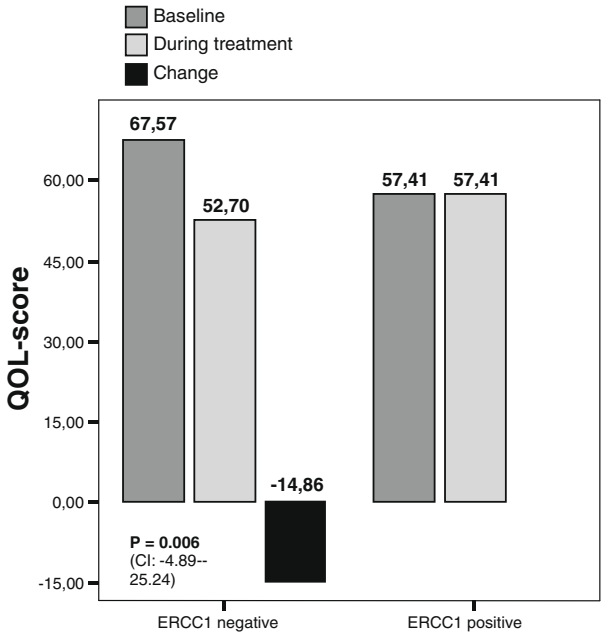

Fig. 3 – Alteration in selfreported quality of life (QOL) among 46 patients with advanced non-small cell lung cancer (NSCLC, adenocarcinoma subtype) stratified according to the excision repair cross complementation group 1 (ERCC1) tumour-marker status.

et al.[28] found significantly increased CTC grade 3/4 GI-toxicity among patients with the ERCC1-C8092A SNPs (C/A and A/A), although information on survival was not available. By using real time RT-PCR Cobo and colleagues[4] found significantly more neurotoxicity and improved RR in ERCC1-neg patients in a large prospective study randomizing 444 patients to +/− platin-based on ERCC1-status. However, more episodes of febrile neutropenia occurred in the control arm than the genotype arm. Booton and colleagues[12] found increased rash in patients with ERCC1-neg tumours but no difference in survival, also using real time RT-PCR.

Looking to other solid tumours ERCC1-status and toxicity has also been explored by the use of PCR on SNPs. In CRC Chua and co-workers[14] found no difference in survival or toxicity related to ERCC1 SNPs supported by Marsh and colleagues[17] in a large retrospective study on 914 patients treated adjuvantly after debulking surgery of ovarian cancer. These results were in contrast to the findings of Khrunin and co-workers[15] who demonstrated more nephrotoxicity among patients with the heterozygote ERCC1 SNPs' (19007: T/C and 8092: C/A) compared to the WT. However, no difference in survival was found. Kim and colleagues[16] demonstrated statistically significant increased CTC grade 3/4 neurotoxicity as well as improved survival in 118 ovarian cancer patients with the ERCC1 SNP-8092 carrying the WT-combination.

Regarding hematological toxicity in patients with advanced NSCLC[29] and early breast cancer[30] it has been demonstrated that increased chemotherapy toxicity results in superior outcome until a certain threshold. This could explain the results from our and some of the above mentioned studies. The limitations of our study aside other covariates could contribute to the deterioration of QOL. Slightly more patients with ERCC1-neg tumours are in PS 1 as compared to the patients with ERCC1-pos tumours possibly due to more comorbidity leaving them vulnerable to the side-effects of treatment. Furthermore, the distribution of gender is different in the two populations with more females having ERCC1-neg tumours. It has been hypothesised that NSCLC may be an entirely different disease in women, especially those with adenocarcinoma subtype. These tumours are often less aggressive/more sensitive to treatment possibly due to decreased DNA-repair as indicated by their typical ERCC1-neg status. The overall picture from the above mentioned studies is blurred by different methodologies, malignancies and lack of data regarding QOL.

However, it appears that the survival benefit related to ERCC1-status comes at the prize of increased toxicity possibly resulting in a deteriorating QOL. If confirmed prospectively this novel observation warrants a reliable methodology for ERCC1-status evaluation, careful patient information prior to inclusion in prospective customised chemotherapy trials and prospective validation of both survival benefit and QOL.

Conflict of interest statement

None declared.

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