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Review

The place of excision repair cross complementation 1 (ERCC1) in surgically treated non-small cell lung cancer☆

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Summary

Platinum-based regimens are the cornerstones of therapy in adjuvant and neoadjuvant management of early stage non-small cell lung cancer (NSCLC). However, the survival benefit associated with platinum-based chemotherapy is marginal and therefore adequate patient selection is essential. Excision repair cross complementation 1 (ERCC1) is a key-enzyme in the repair of platinum-DNA adducts that has been demonstrated to influence the response to platinum-based therapy. We performed a systematic review of the literature from 1996 to September 2007 on studies that assessed the role of ERCC1 in resected NSCLC. Overall, nine studies were identified. ERCC1 expression has been assessed by mRNA expression (n = 5) and/or by protein expression (immunohistochemistry) (n = 5). One study assessed ERCC1 status by both methods. In these studies, patients with early stage NSCLC treated by surgery alone survived longer if ERCC1 levels are high (favourable prognostic value of high ERCC1 level). Conversely, patients treated by surgery and who receive chemotherapy, either as adjuvant therapy or for disease relapse, have a better overall survival when ERCC1 levels are low (favourable predictive value of low ERCC1 level). ERCC1 expression might assist in selecting patients who will respond to adjuvant (neoadjuvant) platinum-based chemotherapy. However, further investigation is necessary in order to prospectively confirm these results and to ascertain the most appropriate method of assessment. Thoracic surgeons should participate in this field of research.

Keywords: Non-small cell lung cancer; ERCC1; Thoracic surgery; Prognostic; Adjuvant chemotherapy

1. Introduction

The overall 5-year survival for all stages of non-small cell lung cancer (NSCLC) remains at 15% [1]. Approximately 20—30% of NSCLC patients are eligible for thoracic surgery on the basis of the stage of the disease and medical fitness [2,3]. In this subgroup, the overall survival ranges from 67% for Stage 1A to 39% for Stage 2B [4].

Platinum-based doublets are an essential component of adjuvant therapy in early stage disease for patients with a good performance status (PS) [5—7]. The ability to select patients who will respond to these agents would reduce the percentage of patients who develop significant toxicity without benefit. Many tools have been studied in an attempt to better select patients for chemotherapy with conflicting or disappointing results to date [8]. Recently, the use of excision repair cross complementation 1 (ERCC1) appears to be a possible exception in this area. In fact, much research has focused on the role of the nucleotide excision repair (NER) pathway in which ERCC1 is an essential component.

Cancer is caused by alterations in the DNA of cells or clones of cells resulting in the loss of normal function and uncontrolled cell growth. This can occur spontaneously within the cell or from external sources such as environmental exposure and drugs. DNA abnormalities occur frequently and indeed it is estimated that there are 25,000 bases per human genome per cell damaged each day. This degree of base damage would be incompatible with life if there were not adequate repair mechanisms present [9]. There are at least four repair mechanisms known to attempt to correct the damage to DNA. These are base excision repair (BER), mismatch repair, double strand break repair and the NER pathways. Within these mechanisms, the NER system is essential to repair bulky damage to DNA such as pyrimidine dimers, cross-links and bulky adducts induced by drugs especially platinum chemotherapeutic agents.

The NER pathway, of which ERCC1 is an integral component, is a complex series of enzymes that repairs bulky damage to DNA (Fig. 1) [10]. Platinum-based

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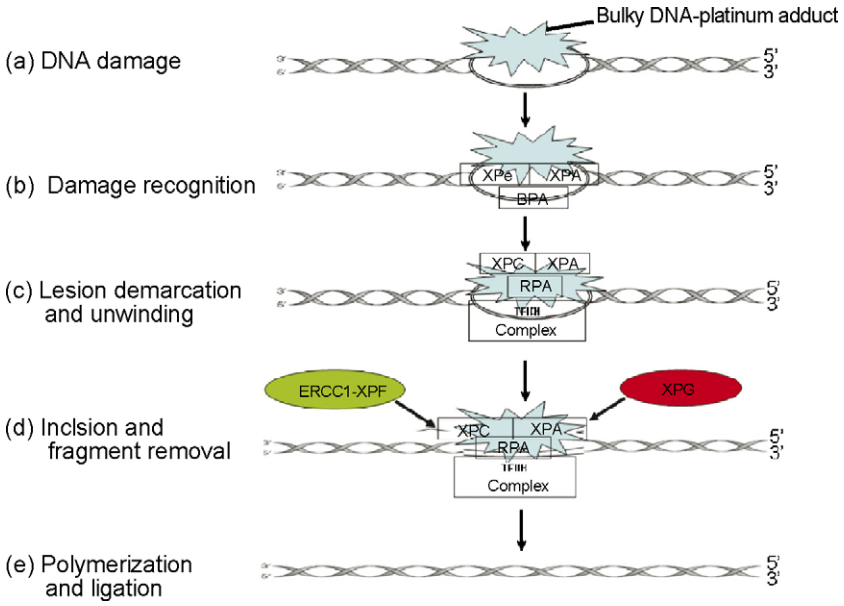

Fig. 1. The core components of nucleotide excision repair. (a) Platinum-based chemotherapy binds to DNA forming bulky adducts. (b) The area of damage is recognised by a protein complex involving XPC, XPA and RPA. (c) The subunit TFIIH complex unwinds the double helix in the vicinity of the base damage creating a bubble in the DNA, the ends of which comprise junctions between the double helix and single stranded DNA. (d) The endonucleases, ERCC1-XPF and XPG cut the damaged strand at the junctions 3′ and 5′ to the site of base damage, respectively, creating an oligonucleotide 27—30 base pairs in length. This includes the damaged base. (e) The nucleotide gap is restored by repair synthesis. XPC, xeroderma pigmentosum complement group C; XPA, xeroderma pigmentosum complement group A; RPA, replication protein a; TFIIH complex, core transcription factor IIH; ERCC1-XPF, excision repair cross complementing 1-xeroderma pigmentosum complement group F; XPG, xeroderma pigmentosum complement group G.

compounds induce their cytotoxic effects by direct binding to both intra- and inter-strand DNA molecules, forming platinum-DNA adduct (pt-DNA adducts), which in turn interferes with DNA transcription and replication, inducing cell death [11]. Removal of pt-DNA adducts is mediated by the NER pathway, which is a coordinated process involving at least 20 enzymes [12]. It is essentially a 'cut-and-paste' repair mechanism [9]. The rate-limiting step in the NER pathway is damage recognition and excision. ERCC1 is the lead enzyme in this process of recognition and excision [13] The ERCC1 gene has a size of 15 kb consisting of 10 exons. It is located on chromosome 19 (19q13.2-q13.3) [10]. It encodes for the ERCC1 protein a structure specific endonuclease which contains 297 amino acids [14].

The predictive and/or prognostic role of ERCC1 in solid tumours, including ovarian, gastric, colorectal and oesophageal carcinomas, has been recognised for the last 10 years [15—21]. These studies revealed that patients with low levels of mRNA expression had better outcomes when treated with platinum-based chemotherapy.

In as much as ERCC1 appears a promising pathway that might be integrated into routine practice [22] we performed a systematic review on the role of ERCC1 in early stage lung cancer; the results of which are presented here.

2. Materials and methods

2.1. Screening of trials

A computerised bibliography was extracted from the Pub-Med database using medical subject headings of the following terms: lung neoplasm, lung cancer, non-small cell lung cancer, early stage disease, thoracic surgery and ERCC1. The search was carried out from October 1996 to September 2007 inclusive. Afterwards, the manual selection of relevant studies was based on summary analysis. In addition to the above-mentioned procedure, bibliographies of selected full papers were screened in order to disclose other relevant articles. Finally, both a manual and an electronic search of available abstracts using the same keywords was undertaken from the latest 'American Society of Clinical Oncology' (ASCO), 2001—2007, the 'International Association for the Study of Lung Cancer' (IASLC), 2001, 2003, 2005, 2007, the 'European Society of Medical Oncology' (ESMO), 2002—2006, and the 'American Association of Cancer Research' (AACR), 2004—2006 were carried out.

2.2. Eligibility criteria

To be included in this review, studies had to fulfil the following criteria: clinical trials reported in the English language involving patients suffering from histologically or cytologically proven early stage NSCLC in which surgery was undertaken and in which analysis of ERCC1, regardless of the technique, was performed.

2.3. Quality assessment

A number of quality-control items within the publications were taken into account, in particular: definition of hypothesis in the statistics section of each article, description of methodology of ERCC1 measurement, definition of the

patients' characteristics in regard to fundamental prognostic factors (sex, performance index, weight loss, stage of the disease), definition of the treatment strategy, surgery preceded or followed by chemotherapy, and/or radiotherapy, and definition of survival, and other relevant outcomes. Studies were also screened regarding the report of response assessment procedure. Finally, the presence of confusing additional variables such as the number of patients lost to follow-up was checked.

2.4. Extraction of data

The following general items were independently recorded by two observers (D.B. and F.B.): year of publication, hypothesis, method of randomisation (where applicable), ERCC1 measurement and statistical analysis. ERCC1 was assessed by different means in the various studies. In brief, these methods included ERCC1 genotyping to identify polymorphisms of the gene, ERCC1 mRNA expression using reverse transcription polymerase chain reaction (RT-PCR) and protein expression based on immunohistochemical techniques. In addition, the following variables were recorded: demographics of the patients: mean age, sex ratio, performance status, clinical stage of the disease. Studies were subdivided into three groups—(i) polymorphisms of ERCC1, (ii) predictive of response to a specific therapy or side effects and, (iii) prognostic of survival. From these three groups, all studies that included surgery as a treatment modality were selected. Data on response rates, partial or complete, time to progression, median survival and overall survival, was recorded when available.

3. Results

The literature search identified 62 articles that may have been relevant to this review. The manual selection of these articles and abstracts excluded 53 studies that did not fulfil the inclusion criteria as detailed above. Studies were excluded if there was replication of results between a presented abstract and publication. In some cases the data was incomplete and therefore it was not possible to interpret the results. This usually occurred when results were presented in abstract form only. In other cases, after review of the abstracts, it became apparent that the article did not address ERCC1 and therefore did not provide relevant data to this review. Finally, studies that examined the role of ERCC1 in advanced disease where surgery was not undertaken were excluded. This resulted in a total of nine papers that are included in this systematic review.

The results are presented under two separate headings. A section on studies examining the role of ERCC1 as a predictive factor will then be followed by studies that address the role of ERCC1 in a prognostic setting. Where applicable, results will be presented according to stage. It must be noted that this division of the results is artificial and therefore leads to some replication within the sections. However, we believe that it allows for easier presentation of the relevant results.

3.1. ERCC1 as a prognostic factor for survival in surgically treated NSCLC

ERCC1 as a prognostic factor has been examined in seven studies (Table 1). The role of ERCC1 has been assessed by different methods: mRNA has been measured by RT-PCR in five studies [14,23—26] and protein expression by immunohistochemical techniques in three studies [25,27,28]. In the studies investigating mRNA expression levels, three studies have examined expression in tumour specimens, using 18SrRNA as a reference gene [14,23,25]. In the other studies, ERCC1 mRNA was measured in surgical specimens and the gene β-actin was used as a reference gene [24,26].

3.1.1. mRNA analysis studies

Simon et al. reported results for 51 patients who had undergone surgical resection. The specimens were immediately frozen in liquid nitrogen post resection. These patients had IA—IIIB disease [14]. Forty-five of these patients received no adjuvant therapy, five patients received postoperative radiotherapy and one patient received combined adjuvant chemoradiotherapy. The authors demonstrated a median tumoural expression of ERCC1 (ratio ERCC1/18SrRNA) of 54.76 (range 4.96—2008). They reported lower expression of ERCC1 in squamous cell carcinoma when compared to adenocarcinoma (median 26.7 months vs 100.4 months, $p = 0.04$) and demonstrated no significant correlation in ERCC1 expression between tumour and normal tissue ($p = 0.094$). When the group was divided into low and high ERCC1 according to the median level (rounded off to 50), there was a statistically significant difference in overall median survival between patients with an ERCC1 level >50 (94.6 months) compared to patients with an ERCC1 level <50 (35.5 months) ($p = 0.001$, two-sided log-rank test). Multivariate analysis confirmed that an ERCC1 level greater than 50 was an independent and significant factor of a favourable outcome (HR = 0.242, 95% C.I. 0.076—0.773, $p = 0.0168$).

Bepler et al. reported in an abstract form their results of 51 patients who had Stage IA—IIIB NSCLC who were treated by surgical resection alone [23]. The specimens were collected and immediately frozen in liquid nitrogen. They reported a strong correlation between ERCC1 and RRM1 ($p < 0.001$). Only the p value was reported in the abstract. They showed that a high expression of ERCC1 was associated with patient survival ($p = 0.01$). However no data on survival times is provided in the abstract, and final results from this study are still awaited.

In summary, both the studies by Bepler and Simon revealed that a high level of ERCC1 was associated with improved survival in patients where surgery was the primary treatment [14,23].

Zheng et al. examined ERCC1 and RRM1 expression in patients with Stage I NSCLC who had undergone complete surgical resection [25]. The patients did not receive adjuvant or neoadjuvant chemotherapy or radiotherapy. In situ protein expression was performed on a tissue micro array using immunofluorescence combined with automated quantitative analysis (AQUA). This analysis was performed in 184 specimens. In addition, mRNA expression was performed by RT-PCR in 44 patient specimens using 18SrRNA as a reference gene. The tumour specimens were fresh

Table 1
ERCC1 as a prognostic factor for overall survival in surgically resected non-small cell lung cancer patients

Author	Stage (*n*)	Treatment	Technique	HR for death [95%CI] for ERCC1+ve status (or high level)
Simon [14]	I–IIIB (51)	Surgery	RT-PCR (ref:18SrRNA)	0.24 [0.07-0.77], $p = 0.016$
Bepler [23]	I–IIIB (51)	Surgery	RT-PCR (ref:18SrRNA)	NR (*decrease in the of risk death*, $p = 0.01$)
Zheng [25]	I (44)	Surgery	RT-PCR (ref: 18SrRNA)	NR
	I (184)		IHC (AQUA)	(*Improved* OS, $p = 0.01$, *DFS*, *NS*)
Rosell [24]	IIB–IIIB (67)	Neoadjuvant CDDP/GMZ + surgery	RT-PCR (ref: β actin)	1.51 [0.55–4.10], $p = 0.422$
Kondo [26]	I–IV (86)	Adjuvant CDDP/x	RT-PCR (ref: β actin)	NR
Olaussen [27]	I–III (760)	Surgery + adjuvant CDDP/x group	IHC (Neomarkers)	1.16 [0.86-1.56], $p = 0.34$
		Surgery alone group		0.66 [0.49-0.90], $p = 0.009$
Lee [28]	NR (133)	Surgery	IHC (Neomarkers)	NR
			SNPS (C8092A, T19007C)	(*Improved* OS, $p = 0.046$)

All studies were done on surgically resected tumour specimens. RT-PCR, reverse transcriptase polymerase chain reaction; HR, hazard ratio; OS, overall survival; DFS, disease-free survival; NS, non-significant; CDDP, cisplatin; GMZ, gemcitabine; IHC, immunohistochemistry; NR, not recorded. Stage is given according to UICC classification.

frozen, formalin fixed and paraffin-embedded. ERCC1 expression was associated with survival ($p = 0.01$ for overall survival and $p = 0.11$ for disease-free survival). The protein expression of RRM1 was correlated with that of ERCC1 ($p < 0.0001$) in the 184 tumour specimens. Patients were grouped into four categories based around the median scores of RRM1 (median, 40.5) and ERCC1 (median, 65.9) protein expression. Patients with high expression of both ERCC1 and RRM1 had a median disease-free survival and overall survival more than 120 months and this was significantly longer than patients in the other three groups; high ERCC1/low RRM1 (disease-free survival, 51.0 months; overall survival, 56.8 months), low ERCC1/high RRM1 (disease-free survival, 56.0 months; overall survival, 80.0 months) and low ERCC1/low RRM1 (disease-free survival, 61.4 months; overall survival, 66.5 months), $p = 0.01$ for disease-free survival and $p = 0.02$ for overall survival. Interestingly, there was a significant correlation between the protein and mRNA assessment for RRM1 expression (Spearman's rho = 0.41, $p = 0.004$) but not for ERCC1 expression (rho = 0.1, $p > 0.30$).

The study by Kondo et al. enrolled 86 patients with Stage I–IV NSCLC who underwent resection and adjuvant cisplatinum-based chemotherapy [26]. The analysis was performed on paraffin-embedded tumour specimens. ERCC1 expression could be measured in 58 out of 86 specimens. The mean ERCC1 was 1.29 (range 0.17–3.76). Using a cut-off of 1.1, patients could be segregated into poor and good prognosis groups. The five-year survival with high and low ERCC1 was 66.2% and 42.7%, respectively ($p = 0.05$). No data are presented for patients with early stage disease but the authors conclude that high ERCC1 levels conferred a favourable prognosis in completely resected NSCLC patients treated with adjuvant cisplatinum-based chemotherapy.

Finally, Rosell et al. reported their results for 67 patients who had NSCLC Stage IIB–IIIB. These patients received neoadjuvant chemotherapy with cisplatinum and gemcitabine followed by surgery [24]. In this study, both mRNA expression of ERCC1, XPD and RRM1 was measured from formalin fixed and paraffin-embedded surgical specimens. ERCC1 mRNA levels ranged from 2.73 to 12.31 (β-actin as the reference gene). A significant correlation was found between ERCC1 and XPD mRNA expression ($r = 0.48$; $p = 0.0001$) but not between ERCC1 and RRM1 ($r = 0.22$; $p = 0.07$). No significant correlation was observed in median survival when analysis was performed according to ERCC1 mRNA expression. The study demonstrated that patients in the lowest quartile for RRM1 and XPD had a decreased risk of death when compared to patients in the top quartile (RRM1, RR = 0.30; 95% C.I. 0.10–0.91, $p = 0.033$; XPD, RR = 0.40; 95% C.I. 0.12–1.37, $p = 0.145$).

3.1.2. Immunohistochemical analysis studies

In the landmark study by Olaussen et al. [27] patients had Stage I–III disease and had participated in the International Adjuvant Lung Cancer trial (IALT). Patients were randomised after complete resection to either an active treatment arm, cisplatin-based chemotherapy (mainly cisplatinum and etoposide or vinorelbine) or to a control arm (observation only) [29]. The IALT trial enrolled 1867 patients of which ERCC1 was analysed in 761 paraffin-embedded tumour specimens. A standard protocol was used for the immunostaining. A monoclonal antibody (Neomarkers) specific against the full-length human ERCC1 protein was used. They reported that 44% of tumour specimens stained positive for ERCC1. The median number of cells with positive staining was 24% (range 0–100%). ERCC1 positive staining was less common in adenocarcinoma as compared to squamous cell carcinoma (21% vs 70%, $p < 0.001$). When performing survival analysis in the observation-only group, the authors demonstrated that there was a statistically significant improved 5-year survival in patients with ERCC1 positive status as compared to ERCC1 negative status (46% vs 39%, HR for death 0.66; 95% C.I. 0.49–0.90; $p = 0.009$). Conversely, in the chemotherapy arm, there was no prognostic impact of ERCC1 positive staining on 5-year survival (ERCC1 positive, 40%; ERCC1 negative, 47%, HR for death 1.66; 95% C.I. 0.86–1.56; $p = 0.34$) (Table 1).

The study by Lee et al. enrolled 133 patients with NSCLC who were treated with curative surgery alone [28]. The authors performed immunohistochemistry for ERCC1 on formalin fixed, paraffin-embedded tumour specimens. They also analysed mutations in the EGFR gene and two single nucleotide polymorphisms (SNPs) in the ERCC1 gene. The ERCC1 analysis was possible in 130 specimens, of which 80 patients (61.5%) had positive status. Patients with positive expression survived longer; median overall survival, ERCC1

Table 2
ERCC1 as a predictive factor in surgically treated NSCLC

Author	Stage (*n*)	Treatment	Technique	HR [95% C.I.] for ERCC1 −ve status
Olaussen et al. [27]	I—III (760)	Sx + adjuvant CDDP/x vs control	IHC (Neomarkers)	0.65 [0.50—0.86], $p = 0.002$
Azuma et al. [30]	IA—IIIB (67)	Platinum-based Cx for relapse post Sx vs control	IHC (Neomarkers)	0.60 [0.44—0.83][a], $p = 0.001$
Hwang et al. [31]	IIIA, N2 (71)	Neoadjuvant CCRT	IHC (NR)	NR; improved DFS, $p = 0.014$; improved OS, $p = 0.001$.

CDDP, cisplatin; Sx, surgery; CCRT, concurrent chemoradiotherapy; NR, not recorded; IHC, immunohistochemistry; HR, hazard ratio; C.I., confidence interval; DFS, disease-free survival; OS, overall survival.
[a] Adapted from paper.

positive, 2742 days; ERCC1 negative, 1423 days; $p = 0.0463$). SNPs were not associated with expression and had no effect on overall survival.

3.2. ERCC1 as a predictive factor in surgically treated NSCLC

Olaussen et al. also investigated the role of ERCC1 as a predictor in early stage NSCLC [27]. This study examined ERCC1 expression by immunohistochemical methods as a predictor of survival. They reported an overall survival significantly longer for patients with ERCC1 negative tumours who had received adjuvant cisplatinum chemotherapy when compared to the observation group who were treated by surgery alone (56 months vs 42 months, respectively (HR for death, 0.65; 95% C.I. 0.50—0.86, $p = 0.002$ in the ERCC1 negative group) [27]. The adjusted HR for death in the ERCC1-positive group was 1.14 (95% C.I. 0.84—1.55; $p = 0.40$).

One study has examined the role of ERCC1 level in relapsing NSCLC after thoracic surgery [30]. Azuma et al. measured ERCC1 by immunohistochemistry using Neomarker monoclonal antibodies. ERCC1 was analysed in 67 resected tumour specimens. The results demonstrated that patients negative for ERCC1 had a significantly longer median progression-free survival (44 weeks vs 26 weeks, $p = 0.0075$) and overall survival (73 weeks vs 44 weeks, $p = 0.0006$) than those positive for ERCC1. Multivariate analysis confirmed that negative ERCC1 expression was a favourable factor for progression-free survival (HR = 1.37, 95% C.I. 1.06—1.76, $p = 0.01$) and overall survival (HR = 1.65, 95% C.I. 1.21—2.275, $p = 0.002$).

Hwang et al. performed immunohistochemistry on mediastinal nodal tissue (N2) from 71 patients who were treated with neoadjuvant chemoradiotherapy followed by surgery for Stage IIIA N2 NSCLC [31]. ERCC1 expression was positive in 32 of the 71 specimens (45.1%). ERCC1 negative as compared to positive status conferred a survival benefit in this population (disease-free survival, 34.0 months vs 15.8 months, $p = 0.014$; overall survival, 65.1 months vs 20.5 months, $p = 0.001$) (Table 2).

4. Discussion

Adjuvant cisplatin-based chemotherapy is now the standard of care for patients with resected Stage II—IIIA NSCLC [32]. However, the overall survival benefit from preoperative therapy is 6% and 4% from adjuvant chemotherapy [33,34]. It is therefore essential that we attempt to tailor adjuvant therapy to those who are at risk of relapse according to prognostic factors, and those who will respond to a specific treatment, according to predictive factors. The present review highlights the potential role of ERCC1 in customising adjuvant management of resected NSCLC. Indeed, patients whose tumoural level ERCC1 is high spontaneously show a good prognosis when compared with patients with tumours expressing low level of ERCC1. Furthermore, response to platinum-based therapy is unlikely in the setting of high tumoural ERCC1 levels. The results of the IALTbio study [27] have firstly to be supported by ongoing or future studies on tissue samples from patients included in the ANITA [35] and JBR10 trials [36]. Secondly, prospective 'proof of concept' clinical trials (such as the SWOG trial conducted in the USA, the ITACA trial conducted in Italy, and the IFCT trial which might start enrolling soon in France) have to validate the superiority and the safety of such patient selection before ERCC1 expression can be used for routine patient selection for adjuvant platinum-based chemotherapy.

With regard to neoadjuvant therapy, two caveats need to be taken into account. Firstly, it remains unclear if neoadjuvant chemotherapy will become a standard of care in NSCLC and secondly there appears to be discordance between measured ERCC1 from bronchoscopically obtained biopsies and the final surgical specimen, with a discordance rate of 9% in a French study [37]. This study needs to be confirmed in larger cohorts but it does suggest that the use of biomarkers including ERCC1 to tailor preoperative chemotherapy may be appropriate.

Over the last 10 years, the important role of ERCC1 has been suggested in a number of treated solid tumours including ovarian, gastric, colorectal and oesophageal carcinomas [15—21]. These small studies have all suggested an association between low levels of mRNA expression and improved outcomes in patients treated with platinum-based chemotherapy. Using ERCC1 as a tool to select patients for therapy has also been advocated in other cancers. Warnecke-Eberz et al. demonstrated that ERCC1 mRNA expression measured by RT-PCR in pretreatment endoscopic biopsy specimens was specific to predict minor response to neoadjuvant chemoradiotherapy in patients with locally advanced oesophageal cancer and they concluded that this technique could prevent non-effective and toxic therapies in a large proportion (42%) of patients [38]. Metzger et al. has shown that ERCC1 mRNA levels had a statistically significant relationship to response and survival in patients with primary gastric adenocarcinoma treated with neoadjuvant cisplatinum and 5-flourouracil [17].

However, a number of important observations must be highlighted. ERCC1 analysis has been performed by immunohistochemistry and ERCC1 mRNA expression. The relationship between these two techniques of ERCC1 assessment remains uncertain. Indeed, Zheng et al. could not demonstrate a correlation between the ERCC1 mRNA (quantitative, real time RT-PCR) and protein expression (AQUA) [25]. However, the analysis was performed on 44 samples and bigger studies are required to address this issue. The majority of the studies have a retrospective design with inherent bias and most studies have enrolled small numbers of patients which impacts on their power. This leads to difficulties with a direct comparison between the various studies. Therefore, well-designed prospective studies such as ongoing trials described before are still needed to clarify how ERCC1 may be used in selecting NSCLC patients for platinum-based chemotherapy.

Furthermore, besides ERCC1, several key-points inside or outside of the NER pathway such as BRCA1 [39], XRCC3 [40], RRM1 [41], have been described to influence response of NSCLC patients to chemotherapy drugs, such as cisplatin, taxanes or gemcitabine. Therefore, assessment of only one molecular marker such as ERCC1, whatever its validity and reproducibility might be inadequate. The study by Zheng et al. grouped patients according to the level of protein expression of RRM1 and ERCC1 [25]. Some authors have proposed a more global approach to assessing prognosis of early stage NSCLC using DNA array technology [42]. In particular, Potti et al. were able to discriminate different groups of Stage I NSCLC patients with dramatic difference with regard to risk of relapse and overall survival. Once again, these hypotheses have to be confirmed by planned or ongoing trials such as the SCAT trial conducted in Spain and based on BRCA1, and the CALGB trial conducted in the US and based on the lung metagene predictor [42]. However, the factor(s) used to discriminate the patients need to be carefully evaluated as a greater risk of relapse is not necessarily related to the potential response to chemotherapy. Therefore, the tailored management of postoperative treatment is still of concern and prospective trials are always needed.

In conclusion, the data supporting a role for ERCC1 in NSCLC is promising. The studies to date suggest that platinum-based therapy is more efficacious in tumours that express low ERCC1 levels and that alternative non-platinum-based therapy or observation alone may be a better option in patients with tumours expressing high ERCC1 level. However, confirmatory retrospective analyses as well as prospective randomised trials are needed before putting ERCC1 in daily practice for treatment making-decision.

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