ERCC1 influence on the incidence of brain metastases in patients with non-squamous NSCLC treated with adjuvant cisplatin-based chemotherapy

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Background: We recently demonstrated that excision repair cross-complementing group 1 protein (ERCC1) is predictive of adjuvant cisplatin-based chemotherapy benefit in resected non-small-cell lung cancer (NSCLC). Non-squamous cell carcinomas (non-SCCs) carry an increased risk of brain metastases (BMs). We hypothesised that there might be an increased incidence of BMs in ERCC1-negative non-SCCs when treated with adjuvant cisplatin-based chemotherapy.

Patients and methods: Incidence of BMs and histoclinical parameters were analysed in a population of 761 patients enrolled in the International Adjuvant Lung Cancer Trial. A subgroup analysis was carried out in patients with ERCC1-negative non-SCCs.

Results: Of 761 patients, 98 developed BMs alone or in association with other metastatic sites, with a 5-year incidence rate of 18.0% (14.7%-21.8%). In the multivariate analysis, the clinical parameters associated with the occurrence of BMs were the nodal status (P = 0.02) and histological type [give hazard ratio (HR) for non-squamous to quantify introduction assertion, P = 0.002]. Chemotherapy had no effect on BMs [HR = 1.4 (0.90-2.1), P = 0.14]. In patients with non-SCC histology (n = 335), adjuvant chemotherapy was associated with an increased risk of BMs [HR = 2.1 (1.01-4.3), P = 0.04] for ERCC1-negative tumours, whereas there was no evidence of an effect on BMs for ERCC1-positive tumours [HR = 1.1 (0.38-3.0), P = 0.90]. Nevertheless, these two effects are not different (P = 0.30 for interaction) possibly due to a lack of power in this subgroup.

Conclusions: This study suggests that adjuvant cisplatin-based chemotherapy is associated with an increased risk of BMs in patients with resected chemosensitive non-SCCs. If confirmed, these data could provide a rationale for new follow-up and/or prophylactic strategies.

Key words: adjuvant chemotherapy, brain metastasis, cisplatin, ERCC1, lung cancer, randomised trial

introduction

Lung cancer remains the leading cause of cancer death both in the United States and worldwide [1]. The standard of care for localised non-small-cell lung cancer (NSCLC) is surgery followed by, in case of stage II and III disease, adjuvant cisplatin-based chemotherapy. The Lung Adjuvant Cisplatin Evaluation program, a pooled analysis of the five largest trials, recently showed an absolute 5-year survival benefit of 5.3% with adjuvant chemotherapy as well as the NSCLC meta-analysis [2, 3].

In the International Adjuvant Lung Cancer Trial (IALT), 1867 patients were randomly assigned to receive cisplatin-based chemotherapy versus observation after a complete resection of NSCLC [4]. After a median follow-up of 56 months, overall survival was significantly different between the two arms with a 5-year survival rate of 44.5% in the chemotherapy arm versus 40.5% in the control arm [relative risk = 0.86 (0.76-0.98), P < 0.03]. The effect was no longer significant after a median follow-up of 90 months, with a hazard ratio (HR) of 0.91 (0.81-1.02), P = 0.18 [5], in contrast with two other more recently reported randomised trials even updated with a follow-up of above 9 years for one of them [6-8].

Patients likely to benefit from adjuvant chemotherapy cannot be identified through gender, the histological type, or other clinical variables [3]. Molecular markers have therefore been investigated for their potential predictive value. The IALT-Bio program recently showed that excision repair cross-complementing group 1 protein (ERCC1) was predictive of
survival benefit from adjuvant cisplatin-based chemotherapy in the IALT. Patients with ERCC1-negative tumours derived a substantial benefit from adjuvant cisplatin-based chemotherapy compared with ERCC1-positive tumours. ERCC1-positive expression is a favourable prognostic factor in patients with resected disease that are not treated with adjuvant chemotherapy [9].

In the IALT study, the incidence of either local or distant recurrence was significantly lower in the chemotherapy arm compared with the control arm (P < 0.003 for local and P < 0.03 for distant recurrence) [10]. The brain was the most frequent site of metastasis (30%) and the incidence of brain metastasis (BM) was not significantly different between the two arms (P = 0.61), whereas the incidence of metastases at other sites was significantly lower in the chemotherapy arm compared with the control arm.

BM is a major cause of morbidity and mortality in human malignancies. The incidence of BM is estimated to be ~170 000/year in the United States, 10-fold that of primary malignant brain tumours [11]. It has been reported that between 20% and 40% of patients with systemic cancer will develop metastases involving the central nervous system (CNS) during the course of their disease. In adults, metastases to the brain most commonly arise from primary tumours of the lung (50%–60%), breast (15%–20%), skin (melanoma) (5%–10%), and gastrointestinal tract (4%–6%) [11]. Regarding NSCLC, non-squamous carcinomas, and in particular adenocarcinoma, run an increased risk of BMs after a definitive treatment of localised disease [12–14]. The blood–brain barrier (BBB) is of pivotal importance in maintaining homeostasis in the CNS. In the adjuvant setting, CNS may evade chemotherapeutic drugs using the same barrier [15]. As a result, the BBB may protect from chemotherapy the potential metastatic cells that migrated in the brain. The brain is therefore considered a sanctuary site for chemotherapy.

The purpose of our study, which is part of the IALT-Bio program, was to evaluate the differential incidence of BM in patients treated with chemotherapy according to their ERCC1 status and the pathological type. Since a higher rate of BM has been reported in non-squamous NSCLC [12], we hypothesised that ERCC1 might be a predictor of BM in this particular subgroup. If the incidence of BMs increased in patients with ERCC1-negative disease, it could indicate a group of patients in which the micrometastatic disease has a higher likelihood to be eradicated by adjuvant chemotherapy, except in the sanctuary brain site.

patients and methods

patients

All patients had participated in the IALT study, which compared adjuvant cisplatin-based chemotherapy with observation in subjects with NSCLC. Inclusion criteria and the results of the IALT have already been reported [4]. Briefly, patients with completely resected stage I-III NSCLC were randomised between February 1995 and December 2000 to either chemotherapy with cisplatin (total dose 300–400 mg/m²) plus an additional drug (etoposide or a vinca alkaloid) or observation (control group). The median follow-up time was 56 months. Paraffin-embedded tumour sample collection was previously described [9]. A central review of pathological samples was carried out.

ERCC1 evaluation

Immunohistochemical analysis of ERCC1 was carried out with the standardised antigen retrieval technique (citrate buffer). The ERCC1 monoclonal antibody from NeoMarkers (1/300) was used. Staining intensity and the percentage of positive cells were taken into account (H score). The ERCC1 status was available for 761 patients of 783.

statistical analysis

The occurrence of BM was collected from the IALT database. Given the data collected in IALT, we took into account only the BMs occurring as a first distant site of recurrence (alone or in association), following or not a local recurrence. The incidence of BM was estimated using the Kaplan–Meier method with censoring of death.

The association between the patient characteristics and the occurrence of BMs was evaluated with a Cox model adjusted on stage, TNM (tumour–node–metastasis), age, gender, histology, World Health Organisation performance status, lymphoid infiltration, pleural invasion, and treatment stratified by centre. A test of interaction was carried out to compare the effect of chemotherapy in patients with ERCC1-negative and ERCC1-positive tumours.

For analyses within histology subgroups, a more parsimonious multivariate Cox model was used, with adjustment on stage, surgery, lymphoid infiltration, and stratification by centre. All reported P values are two sided. Data were analysed with SAS software. Differences were considered statistically significant when P < 0.05.

results

patient characteristics

The characteristics of the patient population were already reported by Olaussen et al. [9]. A total of 426 cases were squamous cell carcinomas (56%), 242 adenocarcinomas (32%), and 93 were of another histological type (12%). Median age was 58 years (range 27–77) and the great majority were males (82%). A total of 389 patients (51%) were randomised to receive adjuvant cisplatin-based chemotherapy, whereas 372 (49%) were randomised to the control group.

incidence of BMs

Of 761 patients, 98 developed BMs alone or associated with other metastatic sites, with a 5-year incidence of 18.0% (14.7%–21.8%) (Figure 1).
prognostic factors for the occurrence of BM
In a univariate analysis, histology was a major prognostic factor for BM (P = 0.002), with a lower rate of BMs for squamous cell carcinoma than for other histologies (Table 1). In addition, the TNM nodal status appeared to be a strong prognostic factor for BM. In multivariate analysis, the incidence of any recurrence in the brain was increased by the presence of nodal disease [HR = 2.6 (0.93–7.2) for N1 tumours and HR = 3.0 (1.4–6.5) for N2 tumours, P = 0.02] independently of histology. Type of surgery and lymphoid infiltration were also independent prognostic factors.

study of the interaction between the chemotherapy effect and ERCC1 (N = 761)
Based on the Cox analysis (Table 2), there was no effect of chemotherapy on the incidence of BM (P = 0.14). The chemotherapy effect was similar in ERCC1− and ERCC1+ patients (P for interaction = 0.39). In addition, there was no prognostic effect of ERCC1 expression (P = 0.94), which did not differ between treated and control patients.

patient subgroup with non-squamous histology (N = 335)
In patients with non-squamous histology (335 patients who developed 58 BMs), adjuvant chemotherapy was associated with an increased risk of BMs [HR = 2.10 (1.01–4.3), P = 0.04] for ERCC1-negative tumours, whereas there was no evidence of an effect on BM for ERCC1-positive tumours [HR = 1.1 (0.38–3.0), P = 0.90] (Table 3 and Figure 2). Nevertheless, these two effects were not different (P for interaction = 0.30) possibly due to a lack of power in this subgroup.

discussion
In the present study, we showed that (i) the nodal status, stage, and histology (lower risk for N0 and squamous cell carcinoma) were strongly predictive of BM, (ii) there was no evidence for a treatment effect on BM, and (iii) in patients with non-squamous histology, adjuvant chemotherapy was associated with an increased risk of BM for ERCC1-negative tumours, but this increased risk was not significantly different from that among ERCC1-positive tumours probably due to a lack of power.

This retrospective study describes one of the largest reported series of patients with early NSCLC treated by surgery with or without adjuvant cisplatin-based chemotherapy, with focus on BM. Of 761 patients, 98 developed BMs alone or they were associated with other metastatic sites, with a 5-year incidence of 18.0% (14.7%–21.8%). In the multivariate analysis, the clinical parameters associated with the occurrence of BMs were the nodal status and histological type. Other studies have already reported that patients with localised lung cancer present a high risk of BMs and correlated to disease stage, histology, and the nodal status [12, 14, 16–19]. Mamon et al. reported a risk of BMs of 53% at 3 years in surgically staged IIIA (N2) NSCLC; 34% of patients relapsed in the brain as their first site of failure [18]. Ceresoli et al. reported a 22% rate of incidence of BM as the first site of recurrence in 112 patients with advanced NSCLC, most of them occurred within 2 years of the initial

<p>| Table 1. Incidence of BM (98 BMs in 761 patients) and patient characteristics (univariate and multivariate analyses) |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Events/ patients</th>
<th>Univariatea P value</th>
<th>Multivariatea P value</th>
<th>Multivariateb HR (95% CI)</th>
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<tr>
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<td>0.001</td>
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<td>3</td>
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<td>4</td>
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<td>0.30</td>
<td>1.10 (0.7–1.7)</td>
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<td>Histological type</td>
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<td>Squamous cell carcinoma</td>
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<tr>
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<td>1.10 (0.7–1.7)</td>
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<td>Performance status</td>
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<td>0</td>
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<td>0.028</td>
<td>0.10</td>
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<tr>
<td>1</td>
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<td>2</td>
<td>10/59</td>
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<td>Pleural invasion</td>
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<td>No</td>
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<td>0.07</td>
<td>0.05</td>
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<td>0.10</td>
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<td>Vascular invasion</td>
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<td>71/539</td>
<td>0.091</td>
<td>0.10</td>
<td>1.10 (0.7–1.7)</td>
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<tr>
<td>Yes</td>
<td>27/222</td>
<td>0.035</td>
<td>0.25</td>
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<td>Lymphoid infiltration</td>
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<tr>
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<td>0.05</td>
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<td>Intense</td>
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<td>0.091</td>
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<td>Surgery</td>
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<tr>
<td>No</td>
<td>66/455</td>
<td>0.028</td>
<td>0.10</td>
<td>1.10 (0.7–1.7)</td>
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<td>Yes</td>
<td>32/306</td>
<td>0.035</td>
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<td>Control</td>
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<td>Chemotherapy</td>
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<td>ERCC1</td>
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<td></td>
<td></td>
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<td>Negative</td>
<td>57/426</td>
<td>0.028</td>
<td>0.10</td>
<td>1.10 (0.7–1.7)</td>
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<td>Positive</td>
<td>41/335</td>
<td>0.035</td>
<td>0.25</td>
<td>1.10 (0.7–1.7)</td>
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Note:
\(a\) Stratified by centre.
\(b\) Categories 3 and 4 grouped for the test.
BM, brain metastasis; HR, hazard ratio; CI, confidence interval; TNM, tumour–node–metastasis; ERCC1, excision repair cross-complementing group 1 protein.
diagnosis [17]. Law et al. showed that multimodality therapy increased the incidence of isolated BM in advanced NSCLC [19]. All these studies reported on excellent locoregional control in advanced NSCLC, with an 80% local control rate and a decrease in the incidence of metastases at distant sites other than the brain. In the study by Andre et al., preoperative chemotherapy yielded a good local control and a decreased risk of visceral metastases (28% versus 38%) in patients with advanced NSCLC (stage IIIA) but was associated with a high rate of BMs (32% versus 18%) and isolated BMs (22% versus 11%) [12]. In addition, the adenocarcinoma subtype was associated with a high rate of BM. Robnett et al. also reported the occurrence of BM in stage II/III NSCLC treated with chemoradiotherapy between 1992 and 1998. Several parameters were associated with a high rate of BM: a late stage (IIIB versus II/IIIA), non-squamous NSCLC, and induction chemotherapy [13]. In a recent paper, Wang et al. reported that 223 patients were treated with surgical resection for stage III-N2 NSCLC [14]. Frequency of BMs in the entire patient population was 38.1% (85/223) and correlated with the number of mediastinal lymph node metastases and with the non-squamous histology. It is therefore possible that patients with localised NSCLC benefit strongly from multimodality therapies (surgery, radiotherapy, and adjuvant or neoadjuvant chemotherapy) and from increased extracranial control, but still run a high risk of BMs.

This study suggests that adjuvant cisplatin-based chemotherapy has no effect on the incidence of BMs, with the exception that it was associated with an increased risk in resected NSCLC patients with non-squamous ERCC1-negative tumours. The apparent increase in CNS disease in patients with non-squamous ERCC1-negative tumours is likely multifactorial. There is no difference of brain incidence between ERCC1-positive and ERCC1-negative tumours in the...
control arm (surgery without adjuvant chemotherapy). It decreases the possibility of a possible inherent biological factor, although it is not ruled out. A treatment-related factor may exist since in these patients with chemosensitive tumours, the extracranial control is better with chemotherapy [10]. Prevention and treatment of BMs have become a central problem because the BBB provides a sanctuary from the effects of cytotoxic chemotherapy. Indeed, the prophylactic effect of chemotherapy on BMs has not been shown. As an example, the rate of BMs in patients that present a pathological complete response (pCR) after neoadjuvant therapies may not differ from those without pCR, although these patients are at lower risk of distant extracranial metastases [20]. In 51 patients, who achieved a pCR after neoadjuvant chemotherapy or chemoradiotherapy for stage III, the most common site of initial recurrence was the brain [21]. A total of 22 (43%) patients developed BM as the site of first failure, which represented 71% of all isolated recurrences, and 28 (55%) patients developed BMs at some point during their clinical course. This is in line with previous report of BMs incidence in stage III patients [12, 14, 16–19].

Recently, patients with human epidermal growth factor receptor-2 (HER2)-positive breast cancer treated with trastuzumab were reported to develop CNS metastases at higher rates, often while responding favourably to treatment. Trastuzumab has been shown to improve survival in this subset of patients [22]. As trastuzumab is a monoclonal antibody, it does not penetrate the BBB. Based on all the previously reported data, it was hypothesised that the high incidence of BMs could be partially due to the fact that trastuzumab allows the control of visceral metastases but fails to control brain micrometastases. Clayton et al. reported that a BM occurred in 23 of 93 patients with HER2-overexpressing metastatic breast cancer [23]. In the same study, the 1-year incidence of BMs was 26%. Overall, all the studies concerning BMs in patients with HER2-overexpressing metastatic breast cancer are consistent and report that 25%–34% of patients will subsequently develop BMs [24].

Our study has several limitations. First, our main finding (increased incidence of BM in ERCC1-negative patients with non-squamous histology who received chemotherapy) may possibly be a statistical anomaly. It is certainly interesting and hypothesis generating but needs further validation in another setting, preferably as part of a prospective trial. Secondly, the specificity of the 8F1 monoclonal antibody directed against ERCC1 has been challenged [25]. However, additional experiments have suggested that, under the conditions that were applied to the immunohistochemical detection of ERCC1 in NSCLCs, the 8F1 monoclonal antibody detects ERCC1 in a specific fashion [26].

Whatsoever, if the data are confirmed, they could provide a rationale for evaluating prophylactic strategies. In localised small-cell lung cancer, where the incidence of BMs is higher than in NSCLC, a meta-analysis of seven randomised trials of prophylactic cranial irradiation (PCI) suggested an improvement in both the rate of BMs and overall survival [27]. Recently, a randomised trial in patients with diffuse small-cell lung cancer reported a decreased incidence of symptomatic
BM and a decrease in overall survival with PCI [28].
Prospective trials in NSCLC with PCI have demonstrated a decrease in
BM without a survival advantage may be due to a poor
global disease control [29, 30]. More recently, the Radiation
Therapy Oncology Group trial 0214 have compared PCI versus
observation in locally advanced NSCLC having completed
definitive treatment of the primary tumour [31]. The
randomisation was stratified on stage, pathology, and the
locoregional treatment. Unfortunately, it has been closed
prematurely in August 2007 due to insufficient recrual after
almost 5 years (only 356 patients has been included of 1058
planned). The overall survival (primary objective) was similar
between the two arms (1-year survival of 76.9% versus 73.6 %,
P = 0.86), but the incidence of BMs was lower in the PCI arm
(1-year incidence of 7.7% versus 18%, P = 0.004). The lack of
benefit in overall survival may be due to the size of the cohort,
but a positive selection of patients based on a biomarker, as
ERCC1, should have been of value. Another option for
prophylactic therapy would consist in using new targeted
therapy inhibitors to prevent BMs. For example, erlotinib,
which is a small molecule that inhibits epidermal growth factor
receptor, is endowed with biochemical characteristics enabling
it to cross the BBB and could therefore prevent the
development of BMs. Finally, an appropriate workup including
brain computed tomography scan or magnetic resonance
imaging could be proposed for those patients in order to early
detect and treat BMs. These data suggest that several
approaches are available to prevent BMs. Moreover, BM
screening strategies could be evaluated and treatment could be
proposed early after the diagnosis of BMs.

conclusions
In conclusion, our data suggest that early lung cancer is
associated with a high rate of BMs and that adjuvant cisplatin-
based chemotherapy is associated with an increased risk of BMs
in patients with resected ERCC1-negative chemosensitive non-
squamous tumours. These data, if confirmed, could provide a
rationale for evaluating prophylactic strategies against BMs in
this subgroup of patients.

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disclosure
The authors declare no conflict of interest.

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