International Journal of Medicine, 12 (1) (2024) 13-16

International Journal of Medicine

Website: www.sciencepubco.com/index.php/IJM

Research paper

Lung cancer, predictive factor and ERCC1

Souad Souilah *

LAB MRNT, Université Alger 1 Benyoucef Benkhedda, Faculté de Médecine, CHU Bab El Oued, Alger, Algeria
**Corresponding author E-mail: souad.souilah@gmail.com*

Abstract

Introduction: Excision repair cross-complementing group 1 (ERCC1) counteracts the cytotoxic effect of cisplatin through its role in DNA repair, and its expression level is a crucial factor for sensitivity to this drug. The objective of this study was to assess the impact of ERCC1 on tumor response and survival in patients with advanced non-small cell lung cancer (NSCLC) treated with a platinum-based regimen.
Methods: Analysis of survival and tumor response based on the expression level of ERCC1 (detected by immunohistochemistry) in a cohort of NSCLC patients followed in a standard care setting.
Results: Among the 77 cases of NSCLC included, ERCC1 expression was low in 64.9% of cases and high in 35.1% of cases. In the 52 patients treated with cisplatin, survival and tumor response were better in the low-expression group compared to the high-expression group: 14.35 months versus 9.49 months, p=0.022; Objective Response: 42.4% versus 0%, p=0.001. No significant difference was found based on protein expression level in patients treated with carboplatin.
Conclusion: ERCC1 overexpression in patients treated with cisplatin predicts a poor tumor response and shorter survival.

Keywords: *Cisplatin; ERCC1; Lung Cancer; Survival; Tumor Response*.

1. Introduction

- More than two-thirds of non-small cell lung cancers (NSCLC) are diagnosed at advanced stages. In the absence of EGFR mutations or the inability to determine their mutational profile, the treatment for these cases relies on a combination of a platinum salt and a third-generation cytotoxic, ± bevacizumab.
- Therefore, cisplatin remains a major component in the management of advanced or localized NSCLC.
- The cytotoxic effect of cisplatin is linked to its ability to form DNA adducts, distorting its structure and triggering cell cycle arrest. Repair mechanisms are required to restore DNA structure, and the nucleotide excision repair (NER) pathway is primarily responsible for repairing intra-strand platinum adducts. However, cellular intolerance to DNA lesions that threaten genome integrity leads to cell death, hence the beneficial cytotoxic effect of platinum salts on tumor cells.
- One essential protein in the NER pathway is excision repair cross-complementing group 1 (ERCC1), which currently appears to be one of the most promising biomarkers for predicting the benefit of platinum-based chemotherapy. Overexpression of this protein is associated with a decrease in cisplatin cytotoxicity.

2. Study objective

- The objective of this study was to assess the impact of the expression level of the ERCC1 protein on tumor response to chemotherapy and the survival of patients with advanced non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapy.

3. Patients and methods

- The study included a total of 77 patients diagnosed with advanced non-small cell lung cancer (NSCLC) at stages III-IV. The enrollment period spanned from January 2011 to June 2013. All patients received chemotherapy that incorporated a platinum salt as part of their treatment.
- The baseline assessment encompassed a comprehensive examination, including clinical evaluation, chest X-ray, bronchoscopic examination, thoracic computed tomography with upper abdominal sections, abdominal ultrasound, and laboratory tests.
- Histological diagnosis was conducted following the criteria of OMS 2004 and ERS/ATS/IASLC 2011, involving assessments of morphology, histochimistry, and immunohistochemistry (IHC).
- The evaluation of ERCC1 expression was performed using immunohistochemistry with Ventana equipment and the ERCC1 Clone 8F1 antibody.

- Multidisciplinary decisions regarding treatment were made during tumor board meetings, considering factors such as TNM stage, histological type, and performance status (PS) of the patients.
- Evaluation criteria for the study included survival, analyzed using the Kaplan-Meier method, and tumor response, assessed according to RECIST criteria (version 1.1).
- The statistical analysis, carried out using IBM SPSS Statistics 20, involved univariate comparisons, utilizing the Chi2 test or Fisher's test, with significance set at $p \leq 0.05$.

4. Results

4.1. Patients' characteristics

Table 1: Patients' Characteristics

Characteristics		ERCC1 High Expression	Low Expression	P
Patients	Number	27	50	
Age	min-max (year)	18-79	28-78	0,815
	Median (year)	60	60,1	
Gender	Female	11,1%	6%	0,425
	Male	88,9%	94%	
Smoking Status	Non-smoker	29,6%	12%	0,147
	Smoker	51,9%	60%	
	Former Smoker	18,5%	28%	
Performans status (PS)	PS=0	3,7%	10%	0,325
	PS=1	96,3%	90%	
Histological Type	Adénocarcinoma	77,8%	72%	0,698
	Squamous Cell Carcinoma NOS	22,2%	26%	
		0	2%	
Stage TNM	Stage III	22,2%	34%	0,281
	Stage IV	77,8%	66%	
Chemotherapy	Cisplatin-Based Chemotherapy	70,4%	66%	0,450
	Carboplatin-Based Chemotherapy	29,6%	34%	

- The median age was 60 years with a male predominance in both groups.
- Active or past smoking was more frequent in patients with high expression, 88% versus 70.4%. Adenocarcinoma histological type and TNM stage IV were predominant in both patient populations, with a slight predominance in subjects whose tumors overexpressed ERCC1.
- The majority of patients had received cisplatin-based chemotherapy, with 52 versus 25 treated with carboplatin. The median number of cycles was three.
- High ERCC1 expression: 35.1%; low ERCC1 expression: 64.9%.
- No significant differences in expression profile were observed based on gender, age, smoking status, and histology.

4.2. Nuclear expression levels of ERCC1 in immunohistochemistry

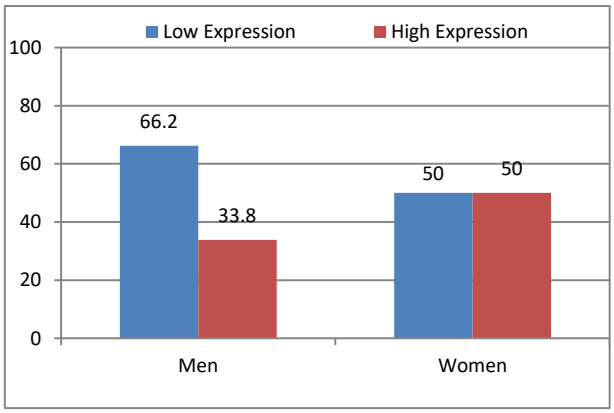

Fig. 1: Nuclear Expression Levels of ERCC1.

4.3. Correlation between ERCC1 expression and survival according to the platinum salt used in chemotherapy

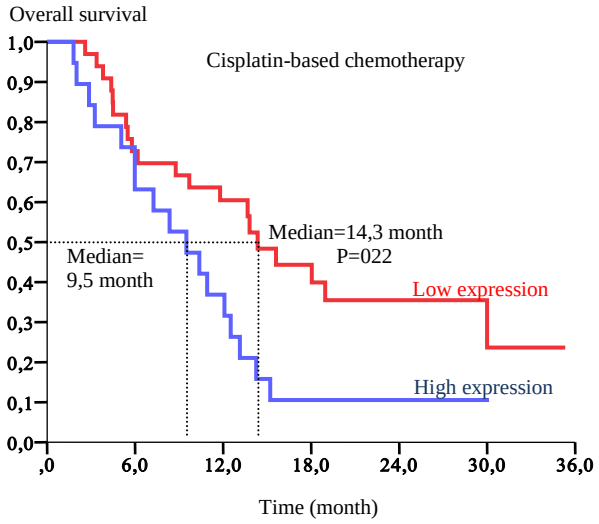

Fig. 2: Overall Survival According to ERCC1 in Cisplatin Chemotherapy.

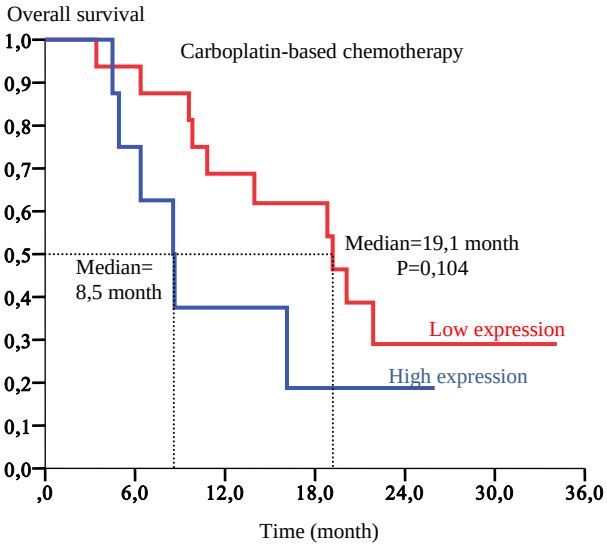

Fig. 3: Overall Survival According to ERCC1 in Carboplatin Chemotherapy.

- In patients treated with cisplatin, survival was better in the low-expression group compared to the high-expression group of ERCC1: 14.3 months versus 9.5 months for medians and 56.4% versus 31.6% for one-year survival rates, p=0.022.
- In patients treated with carboplatin-based chemotherapy, no significant difference was found based on protein expression.

4.4. The relationship between ERCC1 expression and tumor response according to the platinum salt used in chemotherapy

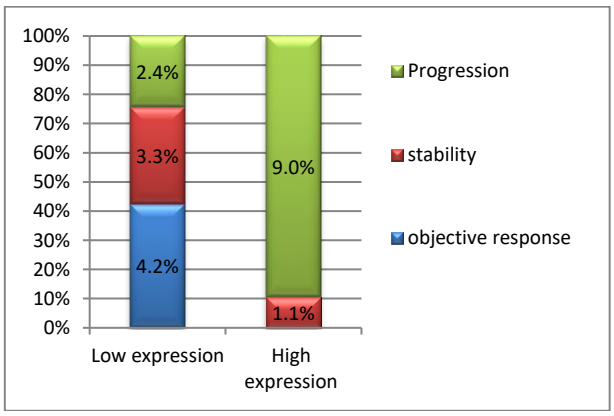

Fig. 4: Tumor Response According to ERCC1 in Cisplatin Chemotherapy.

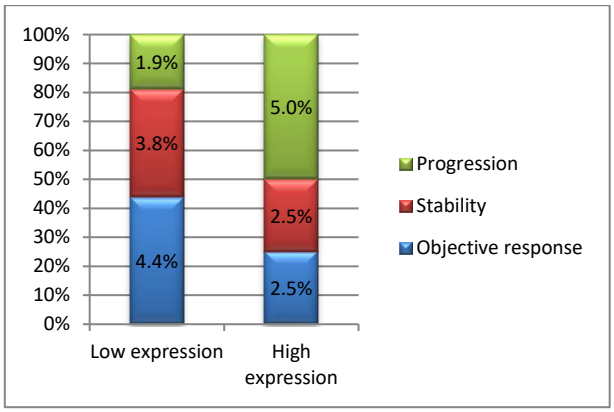

Fig. 5: Tumor Response According to ERCC1 in Carboplatin Chemotherapy.

52 patients received cisplatin-based chemotherapy, while 25 received chemotherapy containing carboplatin.

- For patients who received cisplatin, the rates of objective response and disease control were significantly higher in the low-expression group compared to the high-expression group of ERCC1 (42.4% and 75.7% versus 0% and 10.5%, respectively, P = 0.001).
- In the case of carboplatin-based chemotherapy, objective response rates and disease control were higher in patients with low ERCC1 expression compared to those with ERCC1 overexpression (43.8% and 81.3% versus 25% and 50%, respectively). However, these differences were not statistically significant (p = 0.281).

5. Discussion

- The prognostic and predictive role of ERCC1 has been studied in various works. The IALT study [1], which focused on the contribution of adjuvant chemotherapy, had already demonstrated that survival was better in ERCC1-positive patients in the untreated control group, and it was not improved by platinum-based on adjuvant treatment when ERCC1 expression is high. ERCC1 appears to be a prognostic factor in the absence of treatment (control arm) and predictive in the case of adjuvant chemotherapy in early stages.
- In advanced stages, its predictive role also seems to be confirmed. A prospective phase III study that randomized 444 patients in first-line chemotherapy demonstrated the predictive role of ERCC1 in metastatic stages [2], with a significantly higher response rate in the experimental arm than in the control arm (51.2% versus 39.3%, p = 0.02).
- The results found in the 77 patients of this series show a significant correlation between ERCC1 expression, tumor response, and survival in patients treated with chemotherapy containing cisplatin.
- Survival and response characteristics to chemotherapy containing cisplatin were better in the low expression of ERCC1 group compared to the inverse group. These data confirm the predictive role of ERCC1 in cisplatin-based chemotherapies and are comparable to the majority of published studies on this subject [1-2-3-4-5], where overexpression of the ERCC1 protein is predictive of resistance to platinum salts."

6. Conclusion

Given the observations, which should be further enriched by additional studies, the biological profile of ERCC1 protein overexpression by tumors in the studied patient population shows similarities with international data. The findings also support the concept that overexpression of the ERCC1 protein by tumor cells in patients treated with cisplatin is predictive of a poor tumor response and shorter survival.

Acknowledgements

I am grateful to everyone with whom I had the pleasure of working during the period of this study.

References

[1] KA. Olaussen, A. Dunant, P. Fouret, et al., DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy, The New England journal of medicine, 355, 2006, 983-91. https://doi.org/10.1056/NEJMoa060570.

[2] M. Cobo, D. Isla, B. Massuti, et al., Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer, Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 25, 2007, 2747-54. https://doi.org/10.1200/JCO.2006.09.7915.

[3] S. Chen, J. Zhang, R. Wang, et al., The platinum-based treatments for advanced non-small cell lung cancer, is low/negative ERCC1 expression better than high/positive ERCC1 expression? A meta-analysis, Lung Cancer, 70, 2010, 63-70. https://doi.org/10.1016/j.lungcan.2010.05.010.

[4] B. Holm, A. Mellemgaard, T. Skov, et al., Different impact of excision repair cross-complementation group 1 on survival in male and female patients with inoperable non-small-cell lung cancer treated with carboplatin and gemcitabine, Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 27, 2009, 4254-9. https://doi.org/10.1200/JCO.2008.18.8631.

[5] K. Azuma, Y. Komohara, T. Sasada, et al., Excision repair cross-complementation group 1 predicts progression-free and overall survival in non-small cell lung cancer patients treated with platinum-based chemotherapy, Cancer science, 98, 2007, 1336-43. https://doi.org/10.1111/j.1349-7006.2007.00557.x.