Pharmacological Research 111 (2016) 877–884

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Pharmacogenetic predictors of toxicity to platinum based chemotherapy in non-small cell lung cancer patients

Cristina Pérez-Ramírez[a,b], Marisa Cañadas-Garre (Ph.D)[a,*], Ahmed Alnatsha[c], Eduardo Villar[d], Juan Ramón Delgado[e], María José Faus-Dáder[b], Miguel Ángel Calleja-Hernández[a,f]

[a] Pharmacogenetics Unit, UGC Provincial de Farmacia de Granada, Instituto de Investigación Biosanitaria de Granada, Complejo Hospitalario Universitario de Granada, Avda. Fuerzas Armadas, 2, Spain
[b] Department of Biochemistry, Faculty of Pharmacy, University of Granada, Campus Universitario de Cartuja, s/n, 18071 Granada, Spain
[c] Department of Molecular Medicine, Faculty of Medicine, University of Tübingen, Geissweg 5 72076 Tübingen, Germany
[d] Pathology Service, UGC Anatomía Patológica, Instituto de Investigación Biosanitaria de Granada, Complejo Hospitalario Universitario de Granada, Avda. Fuerzas Armadas, 2, 18014 Granada, Spain
[e] Medical Oncology Service, UGC Oncología Médica, Instituto de Investigación Biosanitaria de Granada, Complejo Hospitalario Universitario de Granada, Avda. Fuerzas Armadas, 2, 18014 Granada, Spain
[f] Department of Pharmacology, Faculty of Pharmacy, University of Granada, Campus Universitario de Cartuja, s/n, 18071 Granada, Spain

ARTICLE INFO

Article history:
Received 2 June 2016
Received in revised form 31 July 2016
Accepted 1 August 2016
Available online 3 August 2016

Keywords:
Platinum based chemotherapy
Non-small cell lung cancer
Toxicity
Polymorphisms

ABSTRACT

Platinum-based chemotherapy is the standard treatment for NSCLC patients with EGFR wild-type, and as alternative to failure to EGFR inhibitors. However, this treatment is aggressive and most patients experience grade 3–4 toxicities. ERCC1, ERCC2, ERCC5, XRCC1, MDM2, ABCB1, MTHFR, MTR, SLC19A1, IL6 and IL16 gene polymorphisms may contribute to individual variation in toxicity to chemotherapy. The aim of this study was to evaluate the effect of these polymorphisms on platinum-based chemotherapy in NSCLC patients. A prospective cohorts study was conducted, including 141 NSCLC patients. Polymorphisms were analyzed by PCR Real-Time with Taqman® probes and sequencing. Patients with ERCC1 C118T-T allele ($p = 0.00345$; RR = 26.05; $CI_{95\%}$ = 4.33, 515.77) and ERCC2 rs50872-CC genotype ($p = 0.00291$; RR = 4.06; $CI_{95\%}$ = 1.66, 10.65) had higher risk of general toxicity for platinum-based chemotherapy. ERCC2 Asp312Asn G-alelle, ABCB1 C1236T-TT and the IL1B rs12621220-CT/TT genotypes conferred a higher risk to present multiple adverse events. The subtype toxicity analysis also revealed that ERCC2 rs50872-CC genotype ($p = 0.01562$; OR = 3.23; $CI_{95\%}$ = 1.29, 8.82) and IL16 rs7170924-T allele ($p = 0.01007$; OR = 3.19; $CI_{95\%}$ = 1.35, 7.97) were associated with grade 3–4 hematological toxicity. We did not found the influence of ERCC1 C8092A, ERCC2 Lys751Gln, ERCC2 Asp312Asn, ERCC5 Asp1104His, XRCC1 Arg194Trp, MDM2 rs1690924, ABCB1 C3435T, ABCB1 Ala893Ser/Thr, MTHFR A1298C, MTHFR C677T, IL1B rs1143623, IL1B rs16944, and IL1B rs1143627 on platinum-based chemotherapy toxicity. In conclusion, ERCC1 C118T, ERCC2 rs50872, ERCC2 Asp312Asn, ABCB1 C1236T, IL1B rs12621220 and IL16 rs7170924 polymorphisms may substantially act as prognostic factors in NSCLC patients treated with platinum-based chemotherapy.

1. Introduction

Lung cancer is the most common diagnosed type of cancer, being the second tumor in incidence, after prostate and breast, respectively. Estimated cases in 2016 are 117,920 in men and 106,470 in women, with an approximate incidence of 14% [1]. This tumor represents the first cause of cancer death worldwide in both genders [1]. According to the latest cancer statistics, over 224,390 new cases and 158,080 deaths are expected to occur in the United States in 2016.

* Corresponding author at: Pharmacogenetics Unit, UGC Provincial de Farmacia de Granada, Instituto de Investigación Biosanitaria de Granada, Complejo Hospitalario Universitario de Granada, Avda. Fuerzas Armadas, 2, 18014 Granada, Spain.
E-mail addresses: cperezramirez87@gmail.com (C. Pérez-Ramírez), marisacgarre@gmail.com (M. Cañadas-Garre), r.j.b-man@hotmail.com (A. Alnatsha), eduardovillar6@gmail.com (E. Villar), juanramondelgado@gmail.com (J.R. Delgado), mfaus@ugr.es (M.J. Faus-Dáder), mangel.calleja.sspa@juntadeandalucia.es (M.Á. Calleja-Hernández).

http://dx.doi.org/10.1016/j.phrs.2016.08.002
1043-6618/

The most important types of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 80–85% of all lung cancer cases and is divided into different subtypes: squamous cell carcinoma, adenocarcinoma and large cell carcinoma. At the time of diagnosis, most patients with NSCLC have advanced stage (IIIB–IV), according to American Joint Committee on Cancer (AJCC) [2–4]. Therefore, five-year survival is low with rates of 5% for IIIB and 1% for IV stages [2–4].

Platinum-based doublet-chemotherapy is the standard treatment for NSCLC for EGFR wild-type patients, and as second line in mutated EGFR patients [5]. It is frequently given together with other agents, such as anti-microtubule agents (taxanes and vinca alkaloids), antifolate agents (pemetrexed), or pyrimidine antagonists (gemcitabine). Platinum-based chemotherapy has showed benefits in terms of survival (10.7 months vs 3.9 months, respectively; $p < 0.001$) and symptom control compared with best supportive care [6,7]. However, it is a very aggressive treatment, which presents high percentages of severe adverse events, such as asthenia (44.0%), gastrointestinal toxicity (33.3%), hematological toxicity (67.1%), neurotoxicity (69.9%) and nephrotoxicity (20–30%) [8–10]. This toxicity profile varies from person to person. Various studies have reported that this inter-individual differences may be due to genetic factors, such as single nucleotide polymorphisms (SNPs), which are involved in platinum pharmacodynamics, metabolism and mechanism of action [11–26].

Cisplatin and carboplatin are the main platinum compounds used on NSCLC therapy. They are heavy metal complexes that interact with DNA, forming platinum-DNA adducts, which result in severe local distortions of the DNA double helix [27,28]. Therefore, this interaction leads to DNA damage, inhibiting DNA replication and transcription and inducing apoptosis. Several pathways are activated in response to this interaction, which include DNA repair and p53 pathways. Deactivation of platinum drugs increase the activity of DNA repair pathways, which involve nucleotide-excision repair (NER), base excision repair (BER), and double-strand break repair (DSB). There are a great variety of proteins involved in detecting and repairing these adducts, such as excision repair cross-complementing group 1 (ERCC1), excision repair cross-complementation group 2 (ERCC2, also known as XPD), excision repair cross-complementation group 5 (ERCC5) and X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) [29,30]. Cell cycle control and apoptosis initiation is mediated by p53 pathway [31]. MDM2 proto-oncogene, E3 ubiquitin protein ligase (MDM2) plays a crucial role in this pathway, because it interacts with p53, leading to its ubiquination and degradation [32]. Genetic alterations, such as SNPs in any of this genes may modulate repair function and apoptosis, promoting individual variation in the toxicity to platinum-based chemotherapy [11–15].

Other mechanisms involved in platinum toxicity are drug transporters, folate metabolism and cytokine signaling [16–24]. Drug transporters are responsible of pumping out the cell platinum compounds [33–35]. The main gene involved in this process is ATP-binding cassette, sub-family B (MDR/TAP), member 1 (ABCB1, also called MDR1). Polymorphisms in this gene may alter its function and expression, leading to an accumulation of platinum drugs outside the cells [36]. Thus, genetic alterations in this gene may affect the inter-individual toxicity profile of platinum-based chemotherapy. Folate metabolism also plays an essential role on platinum cytotoxicity. Polymorphisms in genes involved in this pathway, such as methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MTR) modify methylation of DNA [37–41]. In fact, genetic alterations in these genes have been associated with lower enzyme activity and its results have been correlated with DNA hypomethylation, which alter sensitivity of tumor cells to platinum compounds [23,25,26,42]. Other gene involved in folate metabolism is the solute carrier family 19 (folate transporter), members 1 (SLC19A1). This protein transports folate drugs into the cell, such as pemetrexed, a drug that is frequently given in combination with platinum compounds [20,43]. Polymorphisms in this gene may alter the cellular entry of this drug and subsequently affects the cytotoxicity of platinum-pemetrexed based chemotherapy [18–22]. Citokine signaling has also showed an association with tumor progression [44,45]. Several studies have reported a connection between chronic inflammation and early stage of neoplastic development [46]. Innate immune cells are activated to battle infection as a physiological process. However, if this damaged becomes chronic, it could lead to a continuous cellular proliferation and subsequently initiates metaplasia and dysplasia [44,45]. A family of cytokines, which are named interleukins (ILs), induce growth, differentiation and activation of immune cells [47,48]. Moreover, they inhibit apoptosis of malignant cells at the site of inflammation [48]. In NSCLC, IL1B, IL6 and IL16 have recently showed a relevant impact on clinical outcomes for patients treated with platinum-based chemotherapy [16,17].

Based on above, we conducted this study to evaluate the effects of ERCC1, ERCC2, ERCC5, XRCC1, MDM2, ABCB1, MTHFR, SLC19A1, IL1B, IL6 and IL16 gene polymorphisms in toxicity to platinum-based chemotherapy in NSCLC patients.

2. Material and methods

A prospective cohorts study was conducted.

2.1. Study population

This study was performed at Complejo Hospitalario Universitario de Granada (CHUG), Granada, Spain. Between December 2012 and January 2016, 141 NSCLC patients $\geq$18 years diagnosed histologically or cytologically as NSCLC (stages I–IV) were enrolled in the study. The eligible patients were those with normal results of hematological function (hemoglobin > 9 g/dl, neutrophil count > 1500/mm^3, and platelet count > 100000/mm^3), liver function (bilirubin <1.5 times the normal upper limit, aspartate aminotransferase and alanine aminotransferase <2.5 times the normal upper limit), renal function (creatine clearance rate >50 ml/s) and measurable disease by chest computed tomography (CT) scan.

All patients were treated intravenously with cisplatin or carboplatin in combination with a third-generation drug (gemcitabine, paclitaxel, pemetrexed and vinorelbine) according to the National Comprehensive Cancer Network (NCCN) guidelines [5]. Hematology and biochemistry analyses were done at the end of each cycle. Based on NCCN version 4. 2016 guideline, patients with lymph node metastasis (N2–N3) and distant metastasis (M1) were not surgical candidates, although after neoadjuvant chemotherapy patients with potentially resectable N2 NSCLC were candidates for surgery [5]. Adjuvant chemotherapy was administered in patients with ECOG 0-1. Patients with unresectable stage IIIA NSCLC were candidates for chemoradiotherapy [5].

EGFR status was measured by cobas® EGFR Mutation Test. This study was approved by the CHUG Ethics and Research Committee and was performed conform the declaration of Helsinki. All patients signed an informed consent form for blood sample collection.

2.2. Sociodemographic and clinical variables

Sociodemographic and clinical data were collected by reviewing clinical records. Clinical and histopathological data collected were: gender, family history of cancer, previous non-lung cancer, previous lung disease, smoking status, age, histology, tumor stage, chemotherapy agents, surgery, concomitant or concurrent radiotherapy, EGFR status and response.