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Contribution of genetic factors to platinum-based chemotherapy sensitivity and prognosis of non-small cell lung cancer

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1 TITLE

CONTRIBUTION OF GENETIC FACTORS TO PLATINUM-BASED CHEMOTHERAPY SENSITIVITY AND PROGNOSIS OF NON-SMALL CELL LUNG CANCER

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2 ABSTRACT

Although platinum-based chemotherapy remains as a standard treatment for advanced NSCLC patients, the clinical outcomes are poor and most patients develop high-grade toxicities. Genetic factors, such as single nucleotide polymorphisms (SNPs) involved in platinum pharmacodynamics, metabolism and mechanism of action, may account for inter-individual differences shown in effectiveness and toxicity. Polymorphisms in genes involved in DNA repair and others such as PI3K/PTEN/AKT and TGF-β pathways have been demonstrated to be associated with response, survival and toxicity in advanced NSCLC patients treated with platinum-based chemotherapy. Other cellular processes, like DNA methylation and proliferation have been connected with clinical outcome for platinum-based chemotherapy regimens through folate metabolism and cytokine signaling.

The influence of gene polymorphisms in the NER pathway on clinical outcome has been extensively investigated in advanced NSCLC patients treated with platinum-based chemotherapy but contradictory results have been reported. The most recent and thorough meta-analyses have failed to show an association between *ERCC1* C118T/C8092A and *ERCC5* rs1047768 polymorphisms and response to platinum based chemotherapy. However, other polymorphisms in *ERCC2* (Lys751Gln and Asp312Asn) and *ERCC5* (rs2094258 and rs2296147) and have been related with OS and PFS, respectively. The Arg194Trp and Gln399Arg polymorphisms in *XRCC1*, have also been extensively investigated. Their effects seem to be dependent on ethnicity, and recent meta-analyses have confirmed an association with response in Asian but not in Caucasian patients. The influence on ORR of the rs861539 polymorphism in XRCC3, a protein of the DSB pathway, has also been confirmed in a meta-analysis.

Finally, SNPs in genes coding proteins of the p53, PI3K, TGF-β, membrane transporters, gluthatione metabolism enzymes and cytokine pathways have been less extensively investigated. Some polymorphisms have been reported to be associated with toxicity or clinical outcome, but data generally come from a limited number of studies and need to be confirmed.

3 INTRODUCTION

Lung cancer represents a serious health problem, being the leading cause of cancer mortality among both men and women worldwide, and is the second tumor in incidence (≈14%; only after prostate cancer in men and breast cancer in women) [1]. In the United States, over 224390 new cases and 158080 deaths are estimated in 2015, according to the latest statistics published [1].

Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are the main types of lung cancer. NSCLC represents the great majority, with approximately 80% of all lung cancer cases, and is classified in different subtypes: squamous cell or epidermoid carcinoma, adenocarcinoma and large cell carcinoma. Most patients with NSCLC are diagnosed in an advanced stage (IIIB-IV, according to the American Joint Committee on Cancer) [2-4]. Five-year survival in this stage is poor, with rates of 5% for IIIB and 1% for IV stages [2-4].

The standard treatment for advanced or recurrent NSCLC wild-type for the epidermal growth factor (*EGFR*) gene and not harboring translocations in anaplastic lymphoma receptor tyrosine kinase (*ALK*) is platinum-based chemotherapy, usually in combination with anti-microtubule agents (taxanes and vinca alkaloids), antifolate agents (pemetrexed), or pyrimidine antagonist (gemcitabine). Although this therapy improves survival in comparison with best supportive care [5], response rates (RR) are less than 32%, progression-free survival (PFS) is around 3.5 months and overall survival (OS) 7.4-11.3 months [6-9]. Furthermore, it is a very aggressive

treatment with severe side effects according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4, such as neurotoxic effects (69.9%) or neutropenia (67.1%) [10]. Numerous studies have shown that platinum effectiveness and toxicity varies from person to person and that inter-individual differences may be due to genetic factors such as single nucleotide polymorphisms (SNPs) in particular genes [11-17].

Platinum drugs, particularly cisplatin and carboplatin, are heavy metal complexes that exert their antiproliferative effects by inducing DNA damage. They bind covalently to two different sites, either within the same DNA molecule or between two different DNA molecules, generating adducts that inhibit DNA synthesis and transcription and are responsible for severe toxicity of these drugs [18,19]. Mammalian cells have different DNA repair pathways to repair DNA damage, including nucleotide-excision repair (NER), base excision repair (BER) and double-strand break repair (DSB) (Figure 1). Several proteins of these pathways, 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*), X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*) and X-ray repair complementing defective repair in Chinese hamster cells 3 (*XRCC3*), are involved in the detection and repair of the adducts and cross-links induced by platinum activity [20,21]. The p53 pathway also plays an essential role in DNA repair, together with cell cycle control and apoptosis initiation in response to DNA damage [22]. The *MDM2* proto-oncogene, E3 ubiquitin protein ligase (MDM2) modulates the activity of the pathway through directing binding, ubiquitination and degradation of p53 [23]. Numerous studies have reported that SNPs in any of these genes may regulate the DNA repair functions in the normal and tumor cells, contributing to individual variation in the response and toxicity to platinum-based chemotherapy [11-16,24-27].

Although DNA repair pathways are the key players in platinum toxicity and response, other pathways and proteins are also involved, including the phosphatase and phosphatidylinositol 3-kinase / tensin homolog /v-akt murine thymoma viral oncogene (PI3K/PTEN/AKT) pathway, the transforming growth factor beta (TGF-β) and cytokine signaling pathways, drug transporters, detoxification systems and folate metabolism enzymes. Genetic alterations in genes of the PI3K/PTEN/AKT and TGF-β pathways may modify signaling and have an impact in the development of toxicity or disease progression to platinum-based therapies [28-32]. Polymorphisms in ATP-binding cassette, sub-family B (MDR/TAP), member 1 (*ABCB1*, also called *MDR1*) have also been suggested as predictive markers of response and side effects to platinum therapy [33-35]. *ABCB1* gene is an cell membrane transporter [36], involved in the ATP dependent export of chemicals out of cell [37-39] that modulates response and toxicity by impairing the intracellular retention of multiple anticancer drugs [40,41]. Detoxification of platinum compounds is mediated by glutathione S-transferase Pi 1 (*GSTP1*); gene polymorphisms in this enzyme has been correlated with clinical outcome and toxicity of platinum therapy [42-49]. Methylenetetrahydrofolate reductase (*MTHFR*), methionine synthase (*MTR*) and solute carrier family 19 (folate transporter), members 1 (*SLC19A1*) are involved in folate metabolism [50-54]. Genetic alterations in these genes disturb methylation of DNA, which may influence the effectiveness and toxicity of platinum-based chemotherapy [17,55-57]. Cytokine signaling regulates tumor progression by promoting angiogenesis, cell growth and differentiation of tumoral cells [58]. Finally, gene polymorphisms in interleukin 1B (*IL1B*), 6 (*IL6*), 12A (*IL12A*), 13 (*IL13*), 16 (*IL16*) have also been associated with survival to platinum-based chemotherapy [59,60].

In this review, we will discuss briefly the most relevant gene polymorphisms related with clinical outcomes and toxicity of platinum therapy in NSCLC patients.

4 DNA REPAIR PATHWAYS

Genetic alterations in DNA repair genes can modify individual responses and toxic side effects to platinum-based chemotherapy. Four main DNA repair pathways are utilized by the cells: NER, BER, DBS and MMR (mismatch repair). NER, BER, and DBS are the main repair pathways in the removal of DNA lesions produced by platinum compounds [20,21]. MMR is not directly involved in repair of platinum adducts. It recognizes DNA adducts and activates apoptosis [61]. All of them are regulated by p53, which can trigger cell cycle arrest and DNA repair or apoptosis (Figure 1) [62-65].

4.1 NER PATHWAY

The NER pathway, through *ERCC1*, *ERCC2* and *ERCC5* genes, is able to repair helix-distorting DNA lesions, which prevent base pairing, blocking transcription and normal replication [66-68].

4.1.1 ERCC1

ERCC1 is the key enzyme in the NER pathway [66]. It heterodimerizes with excision repair cross-complementation group 4 (ERCC4 also called XPF), and the resultant ERCC1/ERCC4 complex makes an incision at the 5' end of the lesion, allowing removal of the damaged DNA strand and further polymerization and religation [66,68].

Two polymorphisms in *ERCC1*; rs11615 (C→T synonymous substitution at codon 118, exon 4, Asn→Asn, C118T) and rs3212986 (C→A substitution in the 3'-untranslated region, C8092A); have been extensively investigated in advanced NSCLC patients treated with platinum-based chemotherapy (Table 1) [44,49,69-88]. The possible mechanisms underlying the effects of these base changes in platinum therapy effectiveness and toxicity by is still unclear. Several studies have described some effects on *ERCC1* mRNA expression, whereas others have found no association [89-91].

Regarding *ERCC1* C118T, its association with clinical outcome to platinum-based chemotherapy remains unclear (Table 1) [13,24,44,49,69-88,92-100], with some studies reporting better overall response rate (ORR) in patients carrying the C allele [49,69-72], and others in patients with the TT genotype [44,73-77]. Six meta-analyses have evaluated the influence of *ERCC1* C118T polymorphism [11-13,33,101,102] and the two largest (23 studies/3231 patients and 21 studies/1281 patients, respectively), have not found any association between the ERCC1 C118T polymorphism and ORR (OR=0.94; $CI_{95\%}$=0.72, 1.23; I^2=60%; $P_{heterogeneity}$ <0.01; CT/TT vs CC and OR=0.95; $CI_{95\%}$=0.85, 1.06; I^2=66.90%; $P_{heterogeneity}$=0.386; CT/TT vs CC) [13,102]. The same contradictory results have been reported in the case of PFS and OS, with some studies finding an association of the CC genotype with a better outcome and others reaching opposite conclusions [13,49,70,72,75,77-84,96]. Finally, a meta-analysis including 13 studies, found a significant association of ERCC1 C118T polymorphism with a longer OS (OR=1.26; $CI_{95\%}$=1.02, 1.55; I^2=67%; $P_{heterogeneity}$<0.01; CT/TT vs CC) but not with PFS (OR=1.23; $CI_{95\%}$=0.90, 1.69; I^2=70.7%; $P_{heterogeneity}$ <0.01; CT/TT vs CC) [13].

The *ERCC1* C8092A polymorphism has also been associated with response in two studies in 115 and 163 Asian patients, which reported worse ORR to platinum-based chemotherapy in patients carrying the A allele (OR=0.23; $CI_{95\%}$=0.10, 0.57 for AC/AA vs CC and OR=0.44; $CI_{95\%}$=0.27, 0.74 for A vs C allele, respectively) [72,73]. Studies in Caucasian population have not found significant associations between *ERCC1* C8092A polymorphism and outcome in advanced NSCLC patients [76,87,88,99] and four meta-analyses have reached the same conclusion; the largest one, a meta-analysis carried out with 10 studies and 1311 patients also failed to show influence of this polymorphism on response to platinum-based chemotherapy (OR=1.05; $CI_{95\%}$=0.83, 1.32; I^2=39.3%; $P_{heterogeneity}$=0.096; AC/AA vs CC) [13]. Regarding OS and PFS, results for *ERCC1* C8092A are again contradictory, with some reports associating the CC

genotype with better [72,77,80,85,86] and worse OS and PFS [87,88]. A recent meta-analysis, including 6 studies and 999 cases, could not find any significant association between the polymorphism and OS (HR=1.26; $CI_{95\%}$=0.81, 1.95; I^2=87%; $P_{heterogeneity}$ =<0.01; AC/AA vs CC) [13].

Finally, although the association between toxicity and *ERCC1* polymorphisms has also been extensively investigated, no significant findings have been reported (Table 1) [49,76,79,87,88,91,103-111].

4.1.2 ERCC2

The ERCC2 protein is a component of the general transcription factor IIH (TFIIH) and its helicase activity plays a key role gene transcription and nucleotide excision repair [67].

Numerous SNPs in *ERCC2* gene have been described, being rs13181 (A→C substitution at codon 751, exon 23, Lys→Gln) and rs1799793 (G→A substitution at codon 312, exon 10, Asp→Asp) the most investigated. Although both SNPs cause suboptimal DNA repair capacity [112,113], no significant association has been found between *ERCC2* Lys751Gln or Asp312Asn and ORR or PFS (Table 2) [24,49,73,74,76,79,82,84,87,88,91-93,98,99,104,105,109,114-125]. This lack of association has been confirmed in two recent meta-analyses, including 22 studies/3240 patients [13] and 12 studies/1737 patients [102]. In contrast, several studies have found an association between OS and both SNPs [49,98,118,120]. The genotype CC for *ERCC2* Lys751Gln polymorphism has been correlated with a longer OS compared to the AC/AA genotypes in Asian population (HR=1.54; $CI_{95\%}$=1.03, 2.29; AC/AA vs CC) [118]. In the case of Asp312Asn, the AG/AA genotype has been associated with poor survival both in Caucasian and Asian populations (Table 2) [49,98,118,120]. A meta-analysis has also confirmed these results in Asian (HR=2.07; $CI_{95\%}$=1.11, 3.88; AG/AA vs GG) but not in Caucasian population (HR=0.84; $CI_{95\%}$=0.62, 1.14; AG/AA vs GG) [13].

An relationship between *ERCC2* Asp312Asn and Lys751Gln and hematological toxicity has been reported in two small studies including 55 and 62 patients [79,107], with A-allele for *ERCC2* Lys751Gln associating with increased grade 2-3 neutropenia (p=0.04) [79] and the G-allele Asp312Asn with a reduced frequency of severe hematological toxicity (OR=0.08; $CI_{95\%}$=0.01, 0.40; p=0.0005; AG/GG vs AA) [107].The AA genotype for *ERCC2* Lys751Gln has also been associated with higher risk of severe nephrotoxicity (OR=0.07; $CI_{95\%}$=0.02, 0.31; AC/CC vs AA) [107]. Other studies in larger patient populations (65 to 493) failed to find such associations between *ERCC2* polymorphisms and platinum-based chemotherapy toxicity (Table 2) [49,76,87,88,91,104,105,109,110,117,118,124,126].

Finally, three polymorphisms in *ERCC2* (rs50872, rs238405, rs238416) have been correlated with clinical outcomes in a cohort 1290 Asian advanced NSCLC patients [127], with rs50872 associated with longer OS (p=0.009) and PFS (p=0.032) in all patients, rs238405 in patients treated with a combination of platinum and taxanes and rs238416 in those receiving platinum and gemcitabine doublets [127].

4.1.3 ERCC5

The *ERCC5* gene encodes a single-strand specific DNA endonuclease, which cleaves the damaged DNA strand 3' to the lesion during nucleotide excision repair [128].

The TT genotype in the *ERCC5* rs1047768 polymorphism (T→C substitution at codon 46, exon 2, His→His) has been associated with increased ORR (OR=1.90; $CI_{95\%}$=1.10, 3.28; TT vs CC), OS (HR=0.52; $CI_{95\%}$=0.31, 0.96; TT vs CC) and PFS (HR=0.47; $CI_{95\%}$=0.22, 0.82; TT vs CC) [129]. A meta-analysis which included 5 studies with 846 cases, has recently confirmed these results for ORR (RR=1.23; $CI_{95\%}$=1.11, 1.36 I^2=0%; $P_{heterogeneity}$=0.480; CT/TT vs CC) [102] while no association of rs1047768 with toxicity was found in 74 Spanish NSCLC patients [76]. In

contrast, ERCC5 rs17655 polymorphism (G→C substitution at codon 1104, exon 15, Asp→His) has been related with a higher infection rate (p=0.017) in 388 Chinese NSCLC patients [130] but not with clinical outcome (Table 3) [76,84,93,131-133].

Three additional polymorphisms in *ERCC5* (rs2094258, rs2296147, rs873601) have also been investigated. The G-allele for *ERCC5* rs2094258 has been associated with increased OS (HR=0.51; $CI_{95\%}$=0.39, 0.82; AG/GG vs AA) and PFS (HR=0.44; $CI_{95\%}$=0.34, 0.78; AG/GG vs AA) in 433 advanced NSCLC patients treated with platinum-based chemotherapy [133]. In the case of *ERCC5* rs2296147, two studies in 433 and 277 Chinese patients found a significant association with OS (HR=0.66; $CI_{95\%}$=0.48, 0.99 for CT/TT vs CC and HR=0.49; $CI_{95\%}$=0.36, 0.68 for T vs C allele) and PFS (HR=0.73; $CI_{95\%}$=0.51, 0.97 for CT/TT vs CC and HR=0.52; $CI_{95\%}$=0.38, 0.70 for T vs C allele) [131,133]. Finally, the allele G of the rs873601 polymorphism correlated with a better OS (HR=0.84; $CI_{95\%}$=0.64, 1.09; G vs A allele) in 277 Chinese stage III/IV NSCLC patients [131].

4.2 BER PATHWAY

The BER pathway removes small, non-helix-distorting base lesions from the genome, including single strand breaks produced by oxidation, methylation, deamination and hydroxylation [134]. These lesions may not block transcription and normal replication, but they usually cause miscoding. In this process, the enzymes poly (ADP ribose) polymerase 1 and 2 (PARP1 and PARP2) play a key role, along with apurinic/apyimidinic endonuclease 1 (APE1) and XRCC1 [135,136].

4.2.1 XRCC1

The XRCC1 protein interacts with DNA polymerase-beta, DNA ligase III and PARP (poly ADP-ribose polymerase), repairing the damaged DNA strand [137].

XRCC1 rs1799782 (A→G substitution at codon 194, exon 6, Arg→Trp) and rs25487 (A→G substitution at codon 399, exon 10, Gln→Arg) polymorphisms are the most studied. The T-allele for *XRCC1* Arg194Trp has been associated with better ORR in Asian population, but not in Caucasian patients (Table 4) [76,107,132,138-141]. A recent meta-analysis, which involved 11 studies and compiled 1329 cases, has reported similar results in Asian population (OR=0.38; $CI_{95\%}$=0.30, 0.48; I^2=0%; $P_{heterogeneity}$=0.830; CT/TT vs CC) [15]. For *XRCC1* Gln399Arg, several studies in Asian population have found a relationship between genotype GG and higher ORR (Table 4) [47,97,140,142]. This result has been confirmed by a recent meta-analysis, which evaluated 13 studies and 1334 cases from Asian population (OR=2.05; $CI_{95\%}$=1.62, 2.60; I^2=26%; $P_{heterogeneity}$=0.18; GG vs AG/AA) [15]. However, more recent studies in 325 and 147 Chinese patients have reported poor ORR for GG genotype [43,143]. No significant association has been reported in Caucasian population (Table 4) [49,76,87,88,99,121].

The *XRCC1* Gln399Arg polymorphism has also been associated with OS, PFS and toxicity [42,43,47,99,107,144]. A longer OS for the AA genotype has been reported in two studies in Asian (OR=1.69; $CI_{95\%}$=1.19, 2.39 for GG vs AG/AA and OR=0.17; $CI_{95\%}$=0.06, 0.41 for AA vs GG) and one in Caucasian populations (OR=0.47; $CI_{95\%}$=0.23, 0.95 for A vs G allele) [43,99,144]. The GG genotype showed significant results for PFS in 114 stage-IV NSCLC patients (OR=1.768; $CI_{95\%}$=1.14, 2.73 for AG/AA vs GG) [47] and has also been linked with increased hematological (OR=0.323; $CI_{95\%}$=0.121, 0.862 for AG/AA vs GG and OR=0.22; $CI_{95\%}$=0.06, 0.82 for AG/AA vs GG) and gastrointestinal toxicity (OR=0.298; $CI_{95\%}$=0.108, 0.825 for AG/AA vs GG) [42,107,144]. In contrast, other study reported higher incidence of hematological toxicity for AA/AG genotype (OR=2.135; $CI_{95\%}$=1.207, 3.777 for AG/AA vs GG) [144]. Finally, no associations between OS, PFS, toxicity and *XRCC1* Arg194Trp SNPs have been found (Table 4) [43,76,107,119,129,143,145,146].

4.2.2 PARP1, PARP2 and APE1

The role of *PARP1*, *PARP2* and *APE1* polymorphisms on clinical outcomes to cisplatin in advanced NSCLC has been less investigated. The T-allele for *APE1* rs1760944 polymorphism was found to be associated with gastrointestinal toxicity in 235 patients [144], and the GG genotype for *APE1* rs3136820 showed better OS compared to the TT genotype in 147 patients (HR=0.33; $CI_{95\%}$=0.12, 0.92) [143]. A polymorphism in *PARP1* (rs1136410) has also been associated with survival; in particular, patients with CC genotype showed lower PFS than CT/TT patients (HR=1.90; $CI_{95\%}$=1.02-3.52) [143]. Finally, no studies have evaluated polymorphisms in *PARP2* and their associations with clinical outcomes or toxicity.

4.3 DSB PATHWAY

The DSB pathway is involved in repairing the most severe lesions, affecting both strands, which may result in cell death or a diversity of genetic alterations, such as deletions and chromosomal aberrations [147]. Homologous recombination (HR) and non-homologous end-joining (NHEJ) are the two main mechanisms of the DSB pathway [147]. Key proteins involved are MRE11 (MRE11 homolog A, double strand break repair nuclease), NBN (nibrin) and RAD50 (RAD50 double strand break repair protein), which form the MRE11 complex, BRCA1 (breast cancer 1), BRCA2 (breast cancer 2), RAD51 (RAD51 recombinase) and XRCC3 [147,148]. Despite of the essential function of these proteins in DSB pathway, only a polymorphism in XRCC3 gene has been extensively studied [49,84,92,98,99,105,106,110,117,149-152].

The C→T substitution at codon 241, exon 7 of *XRCC3* (Thr→Met, rs861539) has been associated with ORR and OS, but not with PFS or toxicity (Table 5) [49,84,98,99,105,106,110,117,149-152] The genotype CT/TT has shown higher ORR (OR=2.72; $CI_{95\%}$=1.17, 6.31 for CT/TT vs CC) in 137 Caucasian stage III-IV NSCLC patients [49], a result confirmed by a meta-analysis that included 7 studies and 1186 patients (OR=1.51; $CI_{95\%}$=1.10, 2.07; I^2=0%; $P_{heterogeneity}$=0.618; CT/TT vs CC) [16]. The TT genotype has also been associated with prolonged OS in 135 Caucasian stage III-IV NSCLC patients (OR=0.43; $CI_{95\%}$=0.22, 0.82 for TT vs CC) [92].

5 p53 PATHWAY

The *TP53* tumor suppressor gene regulates the DNA repair through its ability to act as a transcription factor and to interact with damaged DNA, promoting the activation of DNA repair mechanisms [153,154]. In addition, *TP53* may induce apoptosis, arresting the cell cycle progression, when DNA damage is extensive [155,156] (Figure 1).

5.1 TP53

The *TP53* tumor suppressor gene has a prominent role in carcinogenesis [156]. It has an anti-cancer function, inhibiting angiogenesis, inducing apoptosis of tumor cells and maintaining genomic stability [156]. This gene is frequently somatically mutated in NSCLC (40-70%), which may modify p53 activity and induce resistance to platinum based chemotherapy [157].

In tumor cell lines with a wild type *TP53* gene, the GG genotype of a common *TP53* polymorphism located at codon 72, exon 4 (C→G, rs1042522, Pro72Arg), enhances the risk of death by promoting the mitochondrial localization of p53 [158]. When the p53 protein is mutated, the polymorphism has the opposite effect [159,160]. In NSCLC patients treated with platinum compounds, the p53 mutant protein with GG genotype has been described to abolish the function of p73, a related p53 protein, and therefore inhibit apoptosis [24]. The CC genotype has shown better response (OR=3.02; $CI_{95\%}$=1.77, 5.18; CC vs GG) in 640 NSCLC patients treated with platinum compounds [24] while the GG variant has been associated with higher gastrointestinal toxicity (OR=0.24; $CI_{95\%}$=0.076, 0.810 for GC/CC vs GG) (Table 6) [25].

5.2 MDM2

The MDM2 protein is a negative regulator of p53 that binds to the p53 protein inducing its ubiquitination and degradation [23]. Two polymorphisms in *MDM2* (C→T, rs1470383 and A→G, rs1690924) have been associated with gastrointestinal and hematological toxicity, but not with OS and PFS in 663 Chinese NSCLC patients (Table 6) [27]. Patients with the AA genotype for MDM2-rs1470383 showed lower hematological chemotherapy-related toxicity than those with the GG genotype (OR=4.10; $CI_{95\%}$=1.73, 9.71 for GG vs AA) [27]. In contrast, the GG genotype for *MDM2* rs1690924 has been related to lower gastrointestinal toxicity (OR=2.32; $CI_{95\%}$=1.30, 4.14 for AG vs AA) (Table 6) [27]. The relationship between these SNPs with response has not been evaluated.

An association has also been found between a SNP in the promoter region of *MDM2* (T→G, rs2279744) and clinical outcomes in NSCLC patients treated with cisplatin/carboplatin [25,26]. The GG genotype correlated with longer OS (HR=1.33; $CI_{95\%}$=1.03, 1.72 for GT/TT vs GG) in 568 NSCLC patients [26] and lower hematological toxicity in 444 Chinese advanced NSCLC patients (OR=2.18; $CI_{95\%}$=1.12, 4.25 for GT/TT vs GG) [25].

6 PI3K/PTEN/AKT PATHWAY

The PTEN/PI3K/AKT signaling is involved in a great variety of cell processes, such as cell proliferation and survival, which may be altered by polymorphisms in the genes that integrate the pathway [161].

6.1 PI3K

The PI3K enzyme catalyzes the conversion of PIP2 into PIP3, activating the downstream AKT signaling [162]. Despite of this key role, none of the polymorphisms studied to date in the *PI3K* gene (A→G, rs7651265; C→G, rs7640662; T→C, rs7621329, A→C rs6443624; G→A, rs2699887) have shown a significant association with clinical outcomes in NSCLC patients treated with platinum based chemotherapy [28]. Only the AA genotype for rs2699887 has been correlated with increased grade 3-4 toxicity in 168 Caucasian stage IIIB/IV NSCLC patients (OR=3.86; $CI_{95\%}$=1.08, 13.82 for GG vs AA) [28].

6.2 PTEN

PTEN, a well-known tumor suppressor gene, codifies a protein phosphatase that hydrolyzes PIP3 and inhibits the PTEN/PI3K/AKT pathway [163,164].Three polymorphisms in *PTEN* (T→A/C, rs2299939; T→G rs12569398, G→C rs12557281) have been evaluated, and only the AA genotype in rs2299939 has been associated with severe toxicity in 168 Caucasian stage IIIB/IV NSCLC patients (OR=0.44; $CI_{95\%}$=0.20, 0.95 for AC/CC vs AA) [28]. The influence of these SNPs on ORR, PFS and OS has not been determined.

6.3 AKT

The AKT protein is the main downstream target of PI3K pathway. It triggers the phosphorylation of a series of intermediates effectors, promoting cell cycle progression, cell proliferation, transcription and cell migration [165-167].

The T allele in the *AKT* polymorphisms rs3803304 and rs2498804 have been associated with longer PFS in advanced NSCLC patients treated with cisplatin-based chemotherapy (HR=0.66; $CI_{95\%}$=0.45, 0.97 for CT/TT vs CC and HR=0.52; $CI_{95\%}$=0.35, 0.77 for GT/TT vs GG, respectively) [28]. In contrast, the GG genotype of AKT rs1130214 have been correlated with shorter PFS in 168 advanced NSCLC patients (HR=0.62; $CI_{95\%}$=0.42, 0.91 for GT/TT vs GG) [28], while it was associated with better OS (HR=2.78; $CI_{95\%}$=1.11, 6.99 for TT vs GG) and PFS (HR=1.48; $CI_{95\%}$=1.02, 2.15 for TT vs GG) in 310 early NSCLC patients receiving cisplatin-based adjuvant

therapy [168]. No association with toxicity has been described in any polymorphism, and ORR has not been evaluated [28].

7 TGF-β PATHWAY

The TGF-β pathway regulates tumorigenesis and tumor progression through its effects on cellular proliferation, survival, angiogenesis and invasion, via cross talk with SMAD transcriptional regulators [32].

The CT/TT genotypes for the SMAD3 polymorphisms rs6494633 and rs11632964 have been associated with better OS (HR=1.20; $CI_{95\%}$=1.01, 1.43 for CC vs CT/TT and HR=1.52; $CI_{95\%}$=1.05, 2.17 for CC vs CT/TT, respectively) in 598 Caucasian stage IIIA/IV NSCLC patients [29]. In contrast, polymorphisms in TGF-β receptor do not seem to be associated with response and survival to platinum based chemotherapy [29].

8 CELLULAR EFFLUX TRANSPORTERS

Proteins involved in drug efflux are responsible of extruding drugs out of the cell [36,40,41] and polymorphisms in the corresponding genes have been associated with efficacy of platinum based chemotherapy in advanced NSCLC.

8.1 ABCB1

ABCB1 is the most extensively studied transmembrane cellular efflux transporter. It belongs to the ATP-binding cassette family, and pumps out the cell an enormous variety of drugs, including platinum compounds [36,40,41]. Polymorphisms in this gene lead to lower expression and activity of ABCB1 protein, increasing levels of drugs outside the cells [169]. Contradictory results have been obtained when analyzing the association of the silent polymorphism rs1045642, (C→T substitution at codon 1142, exon 26, position 3435, C3435T) [169], with ORR to platinum drugs in advanced NSCLC (Table 7) [74,79,103,109,170-172]. Although a meta-analysis, including 5 studies with a total of 379 Asian and Caucasian patients, reported higher ORR for the CC variant (OR=1.82; $CI_{95\%}$=1.17, 2.85; I^2=0%; $P_{heterogeneity}$=0.77; CC vs CT/TT) [33]. The C-allele has also been associated with better OS (HR=0.77; $CI_{95\%}$=1.11, 6.99 for C vs T allele) and PFS (HR=0.62; $CI_{95\%}$=0.38, 1.00 for C vs T allele) in two studies including 160 and 94 advanced NSCLC patients, respectively [34,109]. A correlation with grade 3-4 gastrointestinal toxicity was also initially reported in 62 stage IIIB-IV NSCLC patients (p=0.03) [79], but in further studies failed to confirm it [35,103,109].

A meta-analysis in Asian population, with a total of 3 studies and 96 patients, has reported better ORR for the GG variant (OR=2.61; $CI_{95\%}$=1.44, 4.74; I^2=0%; $P_{heterogeneity}$=0.51; GG vs GT/GA/TT/AA) of a polymorphism in linkage disequilibrium with C3435T SNP (Ala893Ser, rs2032582), which modifies the expression of the ABCB1 protein [33,103]. In contrast, no significant association with toxicity was reported and PFS and OS were not evaluated (Table 7) [103].

Finally, contradictory reports have also been published regarding the silent SNP rs1128503 (Gly412Gly) The C-allele was associated with longer OS (HR=1.53; $CI_{95\%}$=1.11, 2.09 for C vs T allele) and PFS (HR=2.04; $CI_{95\%}$=1.11, 3.77 for C vs T allele) in 160 stage III-IV NSCLC patients [34] while an analysis of 86 stage IIIB-IV NSCLC patients reported shorter PFS for CC genotype (HR=0.541; $CI_{95\%}$=-1.112, -0.117 for CT/TT vs CC) in [35]. No association with toxicity was found and ORR was not studied.

9 GLUTHATHIONE METABOLIC PATHWAY

The glutathione metabolic pathway mediates platinum detoxification through glutathione conjugation [173]. Glutathione S-transferase (GSTPs) enzymes catalyze this process. The major subclasses of GSTs are GSTM1, GSTP1, GSTT1, and GSTA1 [174]; being GSTP1 the most

abundant isoform in the lung and the enzyme mainly involved in platinum detoxification in NSCLC patients [175,176]. A single nucleotide substitution at exon 5 (G→A, rs1695, Ile105Val) has been demonstrated to alter GSTP1 activity [177], with the Val variant being more active against cisplatin and carboplatin compounds [47,49,178]. Several studies have reported that the AG/GG genotypes in rs1695 are associated with better ORR, PFS and OS (Table 8) [42-47] and that the GG genotype correlates with less severe hematological toxicity (p=0.02), but higher neurotoxicity (p=0.01) [48,49].

10 FOLATE METABOLISM

Folate metabolisms is involved in various intracellular processes such as DNA methylation, cell proliferation and synthesis of nucleic and amino acids [179]. Genetic alterations in these genes may disrupt folate metabolism function, inducing DNA hypomethylation and consequently activating proto-oncogenes [180-184]. Thus, polymorphisms in folate metabolism genes may promote tumor development and modify sensitivity of tumor cells to platinum compounds.

10.1 MTHFR

MTHFR is a crucial enzyme in the folate metabolism. Several polymorphisms in this gene lead to a production of an enzyme with decreased activity and their effects have been linked with DNA hypomethylation, therefore influencing platinum therapy outcomes [180-184].

A C→T transition at codon 222, exon 4 (Val→Ala, rs1801133) has been found to be associated with response, survival and toxicity of platinum compounds drugs. A meta-analysis compiling data from 3 studies and 147 patients, both in Asian and Caucasian populations, has shown better response in individuals with TT genotype (OR=1.72; $CI_{95\%}$=1.01, 2.93; I^2=16%; $P_{heterogeneity}$=0.31; TT vs CT/CC) [17]. The TT variant has also been associated with higher OS (p=0.026) and PFS (p=0.012) in 208 Italian stage IIIB/IV NSCLC patients (Table 9) [122]. Likewise, the genotype CC has been correlated with higher hematological toxicity in 1004 Chinese stage III/IV NSCLC patients (OR=0.40; $CI_{95\%}$=0.19, 0.85 for CT vs CC) (Table 9) [185].

Another polymorphism in MTHFR, which results in an A→C substitution at codon 429, exon 7 (Glu→Ala, rs1801131), has also been associated to platinum based chemotherapy outcomes [185]. Carriers of AA genotype presented lower ORR (OR=1.52; $CI_{95\%}$=1.04, 2.23 for AC vs AA), PFS (p=0.03) and higher gastrointestinal toxicity in a study conducted in 1004 Chinese stage III/IV NSCLC patients (OR=0.40; $CI_{95\%}$=0.22, 2.23 for AC vs AA) (Table 9) [185].

10.2 MTR

MTR is an important vitamin B12-dependent enzyme, which catalyzes the final step in folate metabolism [50].

A transition from A to G at position 2756, exon 26 (rs1805087) causes an amino acid change of Asp to Gly, which has been reported to modify enzyme activity and alter DNA methylation processes [186,187]. However, no significant was found with ORR (OR=0.66; $CI_{95\%}$=0.23, 1.89 for AG/GG vs AA) and OS (HR=0.99; $CI_{95\%}$=0.23, 1.89 for AG/GG vs AA) in two studies including 465 I-IV and 101 IIIB/IV NSCLC patients treated with platinum based chemotherapy (Table 9) [56,57].

10.3 SLC19A1

The reduced folate carrier SLC19A1 is responsible for the transport of folate drugs into the cell, such as pemetrexed, a drug that is usually given in combination with carboplatin/cisplatin [188]. Polymorphisms in this gene may modify the passage of this drug into the tumor cell.

A single nucleotide transition (G→A, rs1051266) at exon 2, which induces an Arg→His replacement in codon 27, has demonstrated to alter pemetrexed-platinum combination

efficacy [55]. The GG genotype has been associated with better OS (HR=1.76; $CI_{95\%}$=1.11, 2.78 for AG/AA vs GG) in 136 lung cancer patients (Table 9) [55]. However, no significant associations have been reported for ORR, PFS and toxicity (Table 9) [55,122,189-191].

11 CYTOKINE SIGNALING

The innate immune cells induce inflammation as a physiological process aimed to combat infection. However, chronic inflammation may cause persistent tissue damage and cellular proliferation leading to metaplasia and dysplasia [192,193]. Consequently, there are prominent connections between chronic inflammation, infection and early stage of neoplastic development. Clinical and epidemiological studies have reported that 20% of tumors are associated to chronic infection, 30% associated to tobacco smoking and pollutant inhalation and 35% are related to nutrition [194].

Growth, differentiation, and activation of immune cells are mediated by a family of cytokines referred as interleukins (ILs) [195]. During tumor development, ILs act as autocrine and paracrine growth factors, inhibiting apoptosis at the site of inflammation [58]. *IL* polymorphisms have recently been associated with OS in stage IIIB-IV NSCLC patients receiving platinum based chemotherapy. In the case of the *IL1B* rs1143634 polymorphism, the T-allele has been correlated with better OS (HR=0.78; 95%CI=0.63, 0.98 for CT/TT vs CC) and PFS (HR=0.73; $CI_{95\%}$=0.57, 0.93 for CT/TT vs CC) in 651 Caucasian patients [60]. Likewise, the CC genotype for *IL6* rs1800795 was found to be associated with better OS (HR=1.682; $CI_{95\%}$=1.077, 2.628 for CG/GG vs CC) in 414 Portuguese stage I-IV NSCLC patients [59]. Finally, the CT/TT genotypes for *IL12A* (rs662959) (HR=1.41; $CI_{95\%}$=1.08, 1.83 for CT/TT vs CC), AC/CC for *IL13* (rs1881457) (HR=1.29; $CI_{95\%}$=1.00, 1.66 for AC/CC vs AA) and GG for *IL16* (rs7170924) (HR=0.65; $CI_{95\%}$=0.50, 0.83 for GT/TT vs GG) have been associated with lower PFS in 651 Caucasian stage I-IV NSCLC patients [60].

12 CONCLUSIONS

The influence of gene polymorphisms in the NER pathway on clinical outcome has been extensively investigated in advanced NSCLC patients treated with platinum-based chemotherapy but contradictory results have been reported. The most recent and thorough meta-analyses have failed to show an association between *ERCC1* C118T/C8092A and *ERCC5* rs1047768 polymorphisms and response to platinum based chemotherapy. However, other polymorphisms in *ERCC2* (Lys751Gln and Asp312Asn) and *ERCC5* (rs2094258 and rs2296147) and have been related with OS and PFS, respectively.

The Arg194Trp and Gln399Arg polymorphisms in *XRCC1*, a protein of the BER pathway, have also been extensively investigated. Their effects seem to be dependent on ethnicity, and recent meta-analyses have confirmed an association with response in Asian but not in Caucasian patients. The influence on ORR of the rs861539 polymorphism in XRCC3, a protein of the DSB pathway, has also been confirmed in a meta-analysis.

Finally, SNPs in genes coding proteins of the p53, PI3K, TGF-β, membrane transporters, gluthatione metabolism enzymes and cytokine pathways have been less extensively investigated. Some polymorphisms have been reported to be associated with toxicity or clinical outcome, but data generally come from a limited number of studies and need to be confirmed.

In summary, we suggested that those polymorphisms in genes most extensively studied such as ERCC2, XRCC1 and XRCC3 may be used in the future as a prognostic and predictive biomarkers informing patient care. ERCC1 C118T/C8092A gene polymorphisms may also be used in clinical practice after clarifying the conflicting results that may be based on the heterogeneity of the population. Polymorphisms in genes belonging to TP53, PI3K, TGF-β pathways, membrane transporters, gluthatione metabolism enzymes and cytokine pathways

have showed an influence on clinical outcomes of NSCLC patients treated with platinum-based chemotherapy but the sample size is insufficient to confirm its effect on clinical outcomes of platinum-based chemotherapy. Thus, further examination involving a large homogeneous sample size (stratified by gender, age and smoking status) and longer follow up is required for these polymorphisms.

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Graphical Abstract

Figure 1. DNA repair pathways involved in removal DNA lesions produced by platinum compounds.