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Editorial

Single Nucleotide Polymorphisms (SNPs) in Non-Small Cell Lung Cancer (NSCLC) Patients

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A single nucleotide polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes in an individual. The majority of cancer genomic projects focus on tumor-specific somatic alterations (mutations). However, structural variations found in the tumor and in normal matched DNA (SNPs) can also contribute as genetic factors that can modify a patient's response to chemotherapy or targeted therapies, as well as determine the kind and severity of side effects experienced. SNPs can be examined in constitutional DNA, such as that retrieved from peripheral blood cells.

SNPs may fall within coding sequences of genes, noncoding regions of genes, or the intergenic regions (regions between genes). SNPs within a coding sequence do not necessarily change the amino acid sequence of the protein that is produced because of redundancy in the genetic code. The taxonomy of SNPs refers to homozygous when both alleles are the same and heterozygous when the alleles are different. For example, in the *ERCC1* C8092A polymorphism, the frequencies of the *C/C*, *C/A*, and *A/A* genotypes have been found to be 53%, 41%, and 6%, respectively [2]. One homozygous variant of *ERCC1* C8092A is *C/C*, the heterozygous variant is *C/A*, and the other homozygous variant is *A/A*. The latter can be considered the minor allele variant.

Chemotherapy induces oxidative stress, reducing both the proliferation and survival rates of cancer cells and yielding an objective treatment response that can be quantified radiographically on the basis of a tumor volume change. However, chemotherapy also affects normal cells, thereby producing toxic side effects [1]. The potential predictive value of SNPs in the response or resistance to chemotherapy and the severity of its toxicity has been examined in patients with several types of tumors, including non-small cell lung cancer (NSCLC).

Nucleotide excision repair (NER) is a key DNA repair pathway considered to be involved in cisplatin chemotherapy resistance [3]. In the NER pathway, ERCC1 is one of the key downstream components. SNPs in *ERCC1* (specifically C118T and C8092A) have been extensively studied with regard to the efficacy and toxicity of cisplatin-based chemotherapy, as have SNPs in the DNA repair gene *XPD*, also known as *ERCC2* (specifically Lys751Gln and Asp312Asn). None of these have been shown to influence outcomes in stage IV NSCLC patients treated with platinum-based chemotherapy [2, 4, 5]. Neither were *ERCC1* C118T and *ERCC1* C8092A associated with hematologic toxicity. However, the presence of the minor allele variant *ERCC1* C8092A (the *A/A* homozygous variant) has been related to a significantly higher risk for grade 3 or 4 gastrointestinal toxicity (odds ratio, 2.33; $p = .03$) [6].

Genomewide association studies (GWASs), in which patterns of SNPs across patients are analyzed in relation to various disease states, have been useful in identifying potential predictive markers for outcomes. Recently, a GWAS identified the rs1878022 SNP in the chemokine-like receptor to be significantly associated with poor survival outcomes in different cohorts of advanced NSCLC patients treated with platinum-based chemotherapy [7]. That study also demonstrated a better survival outcome among patients carrying the homozygous major allele than among those with the heterozygous genotype and the minor allele.

This issue of ***The Oncologist*** features a study from Qian et al. [8] that identifies SNPs in genes encoding caspase-8 and caspase-10 that predict toxicity to cisplatin-based chemotherapy. Caspase-8 and caspase-10 are involved in cell apoptosis

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and form the death-inducing signaling complex that initiates, or activates, effector caspases such as caspase-3, caspase-6, and caspase-7. Qian et al. [8] also comment that caspase-8 and caspase-10 are involved in the TP53-dependent response to cisplatin treatment seen in NSCLC patients, as reported in other studies. Of the SNPs examined in 663 Chinese NSCLC patients, the minor allele of caspase-8, called rs12990906, was notable for its association with a lower rate of severe hematologic toxicity (odds ratio, 0.45; $p = .004$) [8]. It is notable that the exact function of this SNP is not yet known.

SNPs from other apoptosis-related genes have been examined in NSCLC patients. Activation of the proapoptotic molecules BAX and BAK by Bcl-2–interacting mediator of cell death (BIM) permeabilizes the mitochondrial outer membrane, resulting in the release of apoptogenic factors such as cytochrome c, which activates caspases and elicits apoptosis. A deletion polymorphism in intron 2 of the *BIM* gene alters RNA splicing in a manner favoring expression of BIM-Y, a version of BIM lacking the prodeath BH3 domain. This BIM deletion polymorphism was recently examined in 2,597 normal individuals and was detected in 12.3% of east Asians but was not detected in Africans or Europeans, illustrating that some germline variations are related to race. Furthermore, the *BIM* deletion polymorphism was associated with a significantly longer progression-free survival interval in 141 patients with mutant epidermal growth factor receptor (*EGFR*) NSCLC from Singapore and Japan treated with EGFR tyrosine kinase inhibitors (TKIs) [9]. BIM is an upstream component activating BAX and BAK, which ultimately leads to release of apoptotic protease activating factor 1, which leads to stimulation of caspases [10].

Although BIM expression has been found to correlate with outcome in mutant *EGFR* NSCLC patients treated with EGFR TKIs, but not with chemotherapy [11], it could be of interest to examine the *BIM* deletion polymorphism in Asian NSCLC patients. For example, in the large series of Chinese patients in the Qian et al. [8] study, the authors found that caspase-8 rs12990906 was strongly related to chemotherapy toxicity. It would be of interest to screen for caspase-8 rs12990906 among non-Asian NSCLC populations.

Overall, research correlating the presence and frequency of SNPs with clinical outcomes such as the survival time, treatment efficacy, and treatment toxicity remains in its infancy. With the rapid explosion of genetic technology and computing platforms, we will surely see more such studies over the coming years. Classifying patients by their status with regard to key SNPs may be useful for clinical decision making in the future, but currently these studies are strictly knowledge building.

Author Contributions

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