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EVALUATION OF CLINICAL AND ECONOMIC IMPACT OF PHARMACOGENOMICS TESTING IN TAXANES-BASED THERAPY

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Abstract – *Introduction:* *Taxanes are the most common anticancer drugs used to treat several types of neoplasms, such as lung, colorectal, ovarian, breast, head/neck, and genitourinary cancers. However, the efficacy of taxanes-based therapy is often compromised by the severe risk of adverse effects.*

Background: *Pharmacogenomic testing is a promising strategy for cancer management and personalized therapy, allowing stratification of patients for drug response and toxicity, in order to make treatment decisions to maximize benefits and minimize toxicity.*

Materials and Methods: *The search of the MEDLINE, EMBASE and PubMed databases was systematically performed (complete syntax is reported below). Restrictions about the date of publication (1 January 2000 to present day) and language (English) were applied. The references of the resulting issues were also manually considered. Moreover, the cost-effectiveness of the methods used to detect these polymorphisms was taken into account.*

Results: *Several genes that influence pharmacokinetics and pharmacodynamics of taxanes were investigated: members of cytochrome P450 family (CYP2C8, 3A4 and 3A5), β-tubulin (TUBB), Glutathione S-Transferase (GST) and ATP-binding cassette family (ABC). CYP2C8 *3 and *4, CYP3A4 *22 and *1B, GSTP1 and different SNPs in ABCB1 were found to correlate with increased risk of toxicity. Other allelic variants were studied, but the data are often not replicated, or even in contrast, among different authors. Moreover, defining the allelic status of a patient using PCR-based methods allows to significantly reduce global costs.*

Discussion and Conclusions: *Pharmacogenomics markers are constantly increasing and being validated, allowing the physicians to personalize treatments based on the individual genetic profile. Although further studies are needed, the development of a genotyping panel test for clinical practice seems to be more and more realistic.*

KEYWORDS: *Pharmacogenetics, Taxanes toxicity/resistance, Genotyping methods.*

INTRODUCTION

Since Taxol isolation from yews (*Taxus brevifolia*) in 1971, taxanes showed a remarkable anti-cancer activity[1]. Paclitaxel and docetaxel, the first two members of the taxanes family, are widely used as first- or second-line therapy (alone or in combination regimens), to treat different tumors including refractory or metastatic ones[2]. Although these microtubule-stabilizing drugs are very active agents[3], it is not rare to develop adverse effects, especially in the form of hematologic (febrile neutropenia),

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gastro-intestinal (stomatitis) and neurologic (peripheral neuropathy) toxicity[4]. Unfortunately, these adverse effects could reach severe levels (grade ≥ 3), forcing to stop the treatment in about 10-20% of cases[5]. So far, several strategies to prevent adverse effects have been investigated with modest success. Particularly promising are new drug formulations using nano-vector delivery systems[6,7] or albumin-bound paclitaxel (Nab-P)[8,9]. Acute and cumulative toxicity of taxanes are well documented since they could potentially compromise patient benefits. In this sense, pharmacogenomics pursues the aim of predicting, through genotype tests, patients' response towards therapies, allowing physicians to tailor treatments upon each patient's genetic characteristics, reducing toxicity maximizing effects. In this review, we report the late findings on the gene variants known to be involved both in taxanes pharmacokinetics/pharmacodynamics and in the outcome of patients receiving taxanes-containing regimens.

We will also take into consideration the usefulness and the costs of the methods used to detect these genetic alterations for relevant contribution in the cost-effectiveness analysis related to taxanes treatment. We believe that retrospective and prospective studies evaluating the pharmaco-economic impact of genotyping testing in taxane-based therapies could provide strong elements to orientate decision-makers toward the incorporation of PGx testing into daily clinical practice.

MATERIALS AND METHODS

Search strategy and inclusion criteria

A systematic literature search of the MEDLINE, EMBASE and PubMed databases was conducted to identify all studies about taxanes and pharmacogenomics in cancer patient populations from 1 January 2000 to present day. The databases were searched using the following syntax:

I) ((“taxane”[Supplementary Concept] OR “taxane”[All Fields] OR “taxoids”[MeSH Terms] OR “taxoids”[All Fields]) AND (“pharmacogenetics”[MeSH Terms] OR “pharmacogenetics”[All Fields] OR “pharmacogenomics”[All Fields])) AND English[lang]

II) (“paclitaxel”[MeSH Terms] OR “paclitaxel”[All Fields]) AND (“pharmacogenetics”[MeSH Terms] OR “pharmacogenetics”[All Fields] OR “pharmacogenomics”[All Fields]) AND English[lang]

III) (“taxane”[Supplementary Concept] OR “taxane”[All Fields] OR “taxoids”[MeSH Terms] OR “taxoids”[All Fields]) AND (“toxicity”[Subheading] OR “toxicity”[All Fields]) AND (“pharmacogenetics”[MeSH Terms] OR “pharmacogenetics”[All Fields] OR “pharmacogenomics”[All Fields]) AND English[lang]

IV) (“docetaxel”[Supplementary Concept] OR “docetaxel”[All Fields]) AND (“pharmacogenetics”[MeSH Terms] OR “pharmacogenetics”[All Fields] OR “pharmacogenomics”[All Fields]) AND English[lang]

We also manually searched the references of the resulting reviews to identify any relevant pharmacogenomics studies (excluding letters and editorials). In addition, searching was also focused on issues evaluating the pharmacoeconomic impact of genotype testing, likely providing answers for policy making in the incorporation of Pharmacogenomics (PGx) markers into clinical practice.

Toxicity profile

Taxanes are commonly used to treat a wide spectrum of solid tumors such as breast, lung, and ovarian cancers. Therefore, their toxicity profile has been deeply investigated. It is known that patients treated with taxanes (ex. paclitaxel) could develop different moderate/severe adverse effects (grade ≥ 2), forcing modification or even interruption of treatment in about 20% of patients[5]. The administration of taxanes usually induces hematologic toxicity in the form of neutropenia (grade ≥ 2). It is possible to manage this condition by using granulocyte colony-stimulating factor (G-CSF, pegfilgrastim)[10]. The use of some excipients, like Cremophor EL during the infusion of paclitaxel, can lead to severe hypersensitivity reactions. Nevertheless, with the introduction of pre-medication regimens, such as intravenous H1 and H2 antagonists plus corticosteroid therapy (dexamethasone), the occurrence of this kind of reactions was significantly reduced[4]. Unfortunately, one of the less manageable adverse effects that treatment with taxanes could lead is neurotoxicity and in particular peripheral sensorial neuropathy. This form of neuropathy is dose-related, cumulative with doses, and if not treated (even with the suspension of the ongoing chemotherapy regimen), it could progress into an irreversible motor neuropathy. Nowadays it is known, in particular for paclitaxel and docetaxel, that various risk factors for the onset of neurotoxicity exist. We mention dose, schedule and infusion duration, the presence of concomitant pathologies and/or exposure to other neurotoxic agents[11]. Taxanes-induced neurotoxicity is particularly relevant because it represents the adverse effect that more frequently forces oncologists to stop treatments containing taxanes. With

the emergence of pharmacogenomics, it was clear that even little variation in the genome, such as SNPs, could greatly modify pharmacokinetics and pharmacodynamics of virtually all drugs. These genes (described below, and summarized in Table I) are obviously involved in the metabolism, transport, extrusion of the drug from the cells, or they could be the target of the drug itself (β-tubulin). Different SNPs in such genes have been correlated to a higher risk of developing adverse effects, especially neurotoxicity. For all these reasons it is necessary to study in depth the pharmacogenomics aspects on which taxanes toxicity is based, as well as their efficacy and mechanisms of resistance to these chemotherapeutic drugs.

TABLE 1. List of genes (and relative SNPs), known to be involved in taxanes-induced toxicity.

Gene	*dbSNP rs number*	*Activity*	*Description*	*Ref.*
TUBB2A	rs9501929	↓ expression	↑ risk of toxicity	15, 16
	rs909964 rs909965	↑ expression	Lower toxicity	
CYP2C8	*3 rs11572080 *3 rs10509681 *4 rs1058930	↓ metabolic activity	Increased drug exposure → Neurotoxicity (grade ≥2)	16, 22, 23
	Haplotype C rs1113129		Protective genotype	
CYP3A4	*22 rs35599367 *1B rs2740574	↓ metabolic activity due to mRNA instability	Increased risk of peripheral neuropaty	24, 25
CYP3A5	*3 rs776746	↓ metabolic activity due to alternative splicing	Protection against sever toxicity	26
ABCB1 (MDR-1)	rs1045642	↓ expression	Homozygotes have better OS but are more likely to develop hematologic toxicity (grade ≥3)	28
	rs1128503	↓ activity (probably for mRNA instability)	Homozygotes have reduced docetaxel clearance and higher risk of severe toxicity (grade ≥3)	29
	rs2032582	unknown	GG genotypes: less toxicity TT and TA genotypes:	30, 31, 32, 33
GST	GSTP1 rs1695 GSTT1 GSTM1	↓ activity null/null genotypes have no activity	severe toxicities (grade 3≥)	35, 36, 37
ERCC1	rs3212986 rs11615 rs3212935	unknown	Possible association with stomatitis, neutropenia and neurotoxicity	25, 38, 39, 41
ERCC2	rs13181	unknown	↑ risk of severe neutropenia (TT genotype)	
FNCD2	rs7648104 rs7637888 rs6786638 rs6442150	↓ activity (?)	↑ risk of neurotoxicity (grade 3≥)	40
ABCC2/ SLCO1B3	rs12762549/ rs11045585	↓ activity (?)	↑ risk of severe neutropenia (Japanese cohort only)	43
EPHA5	rs7349683	unknown	↑ risk of neurotoxicity; lower cumulative dose to develope neuropathy	16, 46, 47
EPHA6	rs301927	unknown		

Drug-resistance associated to taxanes

Drug-resistance is probably the most difficult challenge that oncology has to face. Cancer cells can possess from the beginning (primary resistance) or develop different resistant mechanisms, under the selective pressure of chemotherapeutics (acquired resistance). Different cellular and molecular mechanisms can lead to unresponsiveness towards a therapy: impairment in drugs metabolism resulting in a decrease of active metabolites and consequently a decrease in drugs effects; alteration in drugs transports inside and/or outside the cells, such as an overexpression of efflux pumps (ABCB1), which cause a decrease in drug concentration within the cells; inhibition or upregulation of apoptotic and anti-apoptotic pathways respectively; increase of DNA repair systems activity (for genotoxic drugs); alterations of the drug targets[12]. In the majority of the cases, these dysregulations are due to allelic variants of the genes which code for proteins involved in the mechanisms mentioned above. Keeping this in mind it seems absolutely necessary a pharmacogenomic approach in order to prevent, or at least limit, the possibility of developing resistance as well as toxicity. Following this concept many polymorphisms in several genes have been studied to find a correlation with resistance/toxicity. Thus, while for some genes (ABCB1) this association is strong, for other genes, (other variants of ABC transporters and tubulins genes), there is not a statistically significant correlation, so further analysis needed. In addition, it has been recently suggested (in prostate cancer) that also micro-RNAs can influence the response to paclitaxel and docetaxel[13]. MiRNAs are short nucleotide sequences (~20-22 bp) which can finely regulate genes expression by leading specific mRNAs degradation. Although it is known that miRNAs are crucial for ensuring a correct gene expression, it is true that an aberrant production of these oligonucleotides can lead to deep modifications in cellular conditions and behaviours. Anyway, to assess miRNAs role in this sense, further studies needed.

Selection of candidate genes and polymorphisms

Quite a few criteria were used to select polymorphisms associated to toxicity/resistance for taxanes (Table 1): A) searching the most validated genetic variants likely providing answers into clinical practice, also SNPs known to influencing the pharmacokinetics/pharmacodynamics of taxanes. (www.pharmagkb.org); B) reviewing the current studies on pharmacogenomics tests available before treatments with taxanes.

β-Tubulin

Taxanes are microtubule-interfering drugs. They act by stabilizing the microtubule apparatus of the cell leading to impairment of chromosomal segregation, cell cycle arrest (G2/M) and thus cell death[14]. The target of taxanes is β-tubulin, one of the two major components for microtubule structures (together with α-tubulin). Several polymorphisms are known in the β-tubulin gene, and some of these can affect protein expression. Response and toxicity in the therapy with taxanes seems to be dependent on the expression levels of β-tubulin. Allelic variants that reduce its expression (rs9501929; −157G in TUBB2A gene) are associated with a higher risk of developing toxicity. A possible explanation for this phenomenon could be found in increased drug exposure due to a drop of its target. On the contrary, SNPs that enhance tubulin expression, such as TUBB2A rs909964 (−101C) and rs909965 (−112G) are associated to a lower toxicity, probably for the apposite of the aforementioned explanation[15]. TUBB2A rs9501929 was found positively correlated to neurotoxicity also by other groups[16].

Class III beta-tubulin (TUBB3) is almost exclusively found in neurons of central and peripheral nervous systems[17]. Since neurotoxicity is a frequent and severe adverse effect, this isoform was particularly interesting. Jung et al[18] reported that the overexpression of TUBB3 could be considered a good biomarker for paclitaxel response. Other groups, such as Yang et al[19], found that high levels of TUBB3 expression were associated with a lower overall response rate (ORR), shorter overall survival (OS), and a worse event-free survival (EFS) in comparison of patients expressing a normal level of TUBB3. Although it is evident that β-tubulin expression can modulate (positively or negatively) response to taxanes, further pharmacogenomics studies are needed because, to date, no SNPs in TUBB3 are known to be associated with taxanes response/resistance.

CYP2C8

Taxanes are primarily metabolized by the liver thanks to Cytochrome P450[20]. It is known that alterations in cytochrome expression strongly affect the pharmacokinetic of virtually all drugs, allowing, in general, stratification of patients in:

poor metabolizers with little or no metabolism; extensive metabolizers which have normal cytochrome activity; ultra-rapid metabolizers, with higher metabolic activity than normal. After this finding, allelic variants of several cytochromes have been deeply analyzed in order to tailor treatments based on patients' metabolic characteristics[21].

CYP2C8, along with CYP3A4, are the main cytochromes involved in taxanes metabolism and their importance has emerged during the last years. Focusing on CYP2C8, it was found that the allele *3 (rs11572080, R139K or rs10509681, K399R) is less functional than the wild-type allele. This causes an impairment in the metabolism (especially for paclitaxel), with the direct consequence of increasing drug exposure till toxic levels (neurotoxicity grade ≥ 2)[22-23]. Other allelic variants have been studied and it seems to exist a link with therapy-related peripheral sensorial neuropathy. Abrahm et al[16] report that allele *4 (rs1058930, I264M) is associated with an increased risk of neuropathy, while other groups report that CYP2C8 haplotype C (rs1113129; G>C) confers protection toward neurotoxicity[5]. In this sense, data are quite concordant that genotyping tests designed to assess CYP2C8 status can be prognostic and/or predictive in taxanes-based therapies.

CYP3A4 and CYP3A5

The two other cytochromes strongly involved in taxanes metabolism are CYP3A4 and CYP3A5 (especially for paclitaxel and docetaxel). The correlation between the allelic variant CYP3A4*22 (rs35599367 C>T in intron 6) and a higher risk of developing peripheral neuropathy has been demonstrated by several groups[24]. It was shown that carriers of CYP3A4*22 have lower hepatic mRNA level than wild-type patients, resulting in a decrease of enzyme concentration and consequently a reduced metabolic activity, leading to an increased and toxic drug exposure (as for CYP2C8).

Kus et al[25] reported that allelic variant CYP3A4*1B (rs2740574; 392A>G), along with ABCB1, can be used as predictive markers for taxanes-induced severe neuropathy, for the same reason as variant *22. Also, recent insights have shown that CYP3A5*3 allele (rs776746, A>G) confers protection against severe toxicity[5]. The molecular explanation for this is still unknown but it seems that this SNP activates alternative splicing resulting in the lower metabolic activity of CYP3A5[26].

ABCB1 (MDR-1)

As mentioned above, one of the drug-resistance mechanisms that tumor cells can use to protect themselves is to avoid drugs exposition. Two ways are possible: I) cells do not have channels, carrier proteins, or they simply are not permeable by drugs, preventing their import; II) cells are permeable by drugs, but they possess surface molecules that allow drugs to be actively pumped outside, preventing their activity. Since drug-unresponsiveness in tumor therapies is a considerable issue, this field has been deeply investigated. The attention was focused on ABCB1, also known as Multi-Drug Resistance protein 1 (MDR-1), the gene which encodes for the P-Glycoprotein (P-Gp). It plays a crucial role in the matter of resistance to several drugs including taxanes. It functions as an ATP-dependent efflux pump for xenobiotics (like toxins or drugs), with the direct consequence of the lower intracellular concentration of drugs[27]. Overexpression of MDR-1 is the strongest predictive biomarker of taxanes and drugs resistance in general. Several polymorphisms are known to date but three of these seems to be statistically relevant in taxanes pharmacogenomics.

ABCB1 rs1045642 (C3435T) is correlated to a lower expression of P-Gp, with the consequent lower efflux of drug from within the cells, and it seems to improve the overall survival. However, the carrier of 3435 TT genotype is more likely to develop severe hematologic toxicity (grade ≥3)[28].

Patients homozygotes for the ABCB1 rs1128503 allele (C1236T) have significantly reduced docetaxel clearance and increased risk of developing a severe toxicity. This is probably due to mRNA instability caused by this SNP, but further studies are needed in this sense[29].

For ABCB1 rs2032582 (G2677T/A; A893S/T) findings are conflicting. In general, GG wild-type genotype seems to confer protection from neutropenia and neuropathy[30,31], while TT and TA genotypes are often found associated with higher hematologic, gastro-intestinal and neurologic toxicities[31,32] as well as with lower PFS in advanced gastric cancers treated with paclitaxel-containing regimens[33]. Anyway, these data are not shared by all groups which have investigated ABCB1 polymorphisms.

GSTP1

Several studies report that an important role in taxanes toxicity is played by Reactive Oxygen Species (ROS), both *in vivo* and *in vitro*[34]. These molecules can damage almost all the structures inside cells and, since their high harmful po-

tential, different protective mechanisms exist. Among these, Glutathione S-Transferases (GSTs) system is widely used by cells to detoxify ROS and several other toxic molecules. Regarding taxanes pharmacogenomics, it is important to report that polymorphisms of this gene are strongly related to increased toxicity. GSTP1, GSTT1, and GSTM1 are the main allelic variants of the GST gene which cause a severe alteration in the expression of this protein. In particular, while GSTP1 (A313G→I105V or C341T→A114V) causes a reduced catalytic activity, GSTT1 and GSTM1 *null/null* genotypes have a complete absence of catalytic activity. All these variants are associated not only with an increased risk of developing certain types of cancers (ex. colorectal)[35], but also with a greater susceptibility in developing severe toxicities (grade 3≥) during different chemotherapy regimens, including those containing taxanes[36,37].

DNA repair genes

Although taxanes are not DNA-damaging molecules, they are commonly associated with drugs which belong to this class, such as platin-based ones. For this reason, pharmacogenetics studies have been conducted to verify if polymorphic variants of genes involved in DNA repair could affect response and/or toxicity in combined taxan and DNA-damaging regimens. However, for this particular class of genes data are quite conflicting. Attention was focused on fundamental genes such as BRCA1 (breast cancer 1), ERCC1/2 (excision repair cross-complementation group 1/2) and XRCC1/3 (X-ray repair cross-complementing protein 1/3).

Bosó et al[38] report that ERCC1 rs3212986 (GG genotype) or ERCC1 rs11615 (TT genotype) are associated with stomatitis and ERCC2 rs13181 (TT genotype) with severe neutropenia, in patients that have lower activity of CYP3A4 and CYP3A5. In addition, they found a correlation between ERCC1 rs3212986 (T allele) and the increased risk of developing grade ≥2 neuropathy.

Kus et al[25] assessed several SNPs in different genes involved in paclitaxel and docetaxel pharmacokinetics and pharmacodynamics, including ERCC1 rs3212935 (A60312G) and the aforementioned ERCC2 rs13181, but the relation with neurotoxicity was not observed.

Another group found a possible association between certain polymorphisms of BCRA1/XRCC1 and response to taxane- and cisplatin-based therapies in the treatment of advanced gastric cancer (regarding OS and PFS). Although patients were numerous (n=200), to consider these genes as prognostic markers for chemotherapy response further studies are needed[39].

Moreover, Sucheston et al[40] analyzed 17 SNPs in this gene but no correlation with toxicity was found. They also selected 20 SNPs for FANCD2 (Fanconi anemia complementation group D2) gene. It is related to DNA damage sensing and repair, and it works associated with BRCA1 and BRCA2. This group report that SNPs rs7648104, rs7637888, rs6786638, rs6442150 are associated with a higher risk of undergoing severe neurotoxicity (grade ≥ 3), and this risk was even higher in the African-American cohort with FANCD2 rs7648104- rs7637888 particular.

In the literature, it is possible to find other issues regarding DNA-repair genes polymorphisms and response/resistance to taxanes-based regimens, but data are often conflicting[41].

Additional candidate gene involved in taxanes therapy

Additional candidate gene variants influencing taxanes-based chemotherapy have been suggested.

ABCC2 (multi-drug resistance protein 2; MRP-2) is involved, as ABCB1, in paclitaxel and docetaxel transport. In vitro, epithelial cells in which ABCC2 is over-expressed are resistant to taxanes, probably because these cells are much more efficient in expelling drugs out of themselves. Anyway even in this case data are quite conflicting[42]. Kiyotani et al[43] report that rs12762549 in ABCC2 and rs11045585 in SLCO1B3 (solute carrier organic anion transporter family member 1B3) are strongly correlated to a higher risk of developing grade ≥ 3 neutropenia in a Japanese cohort, but this datum was not replicated in other populations[38,44,45]. By Genome-Wide Association Study (GWAS) it was possible to find several other genes which could have an important role in taxanes toxicity. Of interest, what result from GWAS analysis is that a particular subfamily of receptors called ephrin type-A receptor (EPHA) may play a role in the pathogenesis of taxanes-induced neurotoxicity. In particular, EPHA5 and EPHA6 are predominantly express in nervous tissues, and SNPs in these genes were positively correlated not only with increased risk of grade ≥2 neurotoxicity (EPHA5 rs7349683; EPHA6 rs301927) but also with a lower cumulative dose of paclitaxel needed to develop sensory neuropathy[16,46,47]. Recently, Fridley et al[48] suggest that certain genetic loci (which include FRAS1, MGC32805, SNCAIP, SLC9A9, TIAL1, ZNF731P, and PCDH20 genes) could be associated with response/resistance to taxanes- and platin-based therapies. Anyway, the mechanisms by which these genes can affect therapy response are still unknown, and it is essential to continue

studies in this sense. Other polymorphisms detected by GWAS are not mentioned in this review due to the lack of a strong validation study. It needed more evidence in future confirmatory studies with other methods and platforms.

Pharmacoeconomic impact of taxanes based therapy

The process of drug-discovery, especially in cancer treatment, is primarily based on a validated multi-trial approach, which often includes the newer expensive patented drugs. On the contrary, a global concept of the healthcare system, in which medical care must be delivered at equal or lower cost with better patient outcomes, is spreading. In this setting, studies evaluating the precise economic impact of taxanes-based treatments are very far from being considered sufficient. In general, it is possible to identify three main types of economic analysis for cancer therapy that differ primarily in the evaluation of health outcome: cost-effectiveness, cost-utility and cost-benefit analysis. In the present case, cost-effectiveness is particularly relevant for its aim: to provide sufficiently robust information for decision-makers to allocate resources to healthcare interventions[49]. The National Institute for Health and Clinical Excellence (NICE), developed and approved a burden disease index called Quality-adjusted life year (QALYs)[50], which is widely used in the matter of economic evaluation for medical interventions. It evaluates several heterogenic information on outcomes, analytical, and cost-effectiveness for each treatment, but essentially it is based on two components: the quantity and quality of life. Construction of such indexes has different aims. First, they allow to identify public health trends and consequently strategies-developing. Second, they allow assessing the effectiveness and efficiency of health care interventions. Lastly, they let to determine the global state of health in communities. The future evolution of these methods, such as QUALYs, will lead to improve personalized treatment and hopefully will shift the balance from disease relapse toward disease eradication.

Evaluation of genotyping costs

It is well known that pharmacogenomics tests, performed before drug treatment, lower overall medical costs and provided higher quality of life and longer life expectancy. Keeping this in mind, it is important to evaluate, with the best esteem, the real cost-effectiveness of a genotype panel test, since this field was never studied in a systematic way before recent days[49]. As a matter of fact, this represents one of the main obstacles of putting into practice pharmacogenomic analysis for clinical purposes, not only in taxanes.

As we report in previous issues, the cost for a genetic test is the sum of different elements: materials and instruments, time-labour, specialized employees, possible genetic counseling, etc. It is possible to commit these tests to custom service or academically referenced laboratories, using commercial kits (if available), but this leads to higher costs (~ 150 € per SNP)[51]. The effort can be lowered as little as ~20 € per SNP, by performing "in house" PCR-based tests (fluorescent probes able to perform allele discrimination assays)[52]. On this basis, a genotype test which evaluates a panel of 5 strategical SNPs will cost no more than 100 € per entire sample processing and analysis (performed in two replicates plus analytical controls), allowing to drastically reduce the expense of manage toxicity and/or change therapy.

The role of genotype testing in the clinical practice is also underlined by Plumpton et al[53] which have recently reviewed several papers about the economic evaluations of pharmacogenetic tests prior treatment with different drugs, providing robust evidence of the cost-effectiveness of this approach. It should be said that it is impossible to define *a priori* the gold standard to detect allele status in genotype testing because it depends on several criteria: 1) detection of known genetic variations; 2) specificity, sensitivity and robustness of the method; 3) availability of large platforms and required equipment; 4) suitability of platforms and tests for routine diagnostics; 5) suitability for high-throughput implementation[54].

Lastly, an issue to consider for the clinical laboratories (who are responsible for providing PGx services), are: i) the availability of FDA-cleared tests; ii) the current absence of public reimbursement; iii) the need for genotyping accuracy; and iv) the need to find clinical expertise to interpret laboratory data results[55,56].

Conclusion and future outlook

Despite the vast amount of studies present in the literature about the issue "taxanes and pharmacogenomics", it still represents a complex topic. For some gene variants like CYP2C8, CYP3A4, ABCB1 and GSTP1 several groups agree in their potential role as predictive biomarkers for taxanes-induced toxicity and response to therapy. Anyway, as for other genes, such as those which belongs to the DNA-repair machinery (BRCA1, XRCC1/2, ERCC1/2), results are not replicated, or even in contrast, especially considering research groups which performed GWAS. Although PGx

and predictive markers allow physicians to improve the efficacy of cancer therapy, reducing toxicity and costs at the same time, we are far from the development of a standard genotype panel test which can be useful for predicting toxicities and/or resistance in taxanes-based chemotherapy regimens. Moreover, even if there is a strong evidence of the potential clinical utility of these described polymorphisms, genotype testing in clinical practice is still strongly limited by the low diffusion of genotyping methods in routine diagnostics and because the cost-effectiveness of this testing is still relatively unknown. In this sense, the usefulness of the described genetic variants for clinical practice is strictly linked to the need of further pharmacogenomics studies, in order to conclusively identify SNPs which really have a role in taxane-mediated toxicity as well as in inter-individual response.

Over the next few years, the emergence of molecular resistance in the new therapies as results of the genomic alterations in cancer will force pharmaceutical and biotechnology companies to develop new tests aimed at tailor treatments upon patients' needs. Therefore, it is fundamental to continue working along this line, to develop standardized methods and valid tests suitable for routine diagnostics in pharmacogenomics, not only for taxanes but also for other chemotherapy regimens[57].

In summary, with the increasing number of novel PGx markers being identified and validated, the oncologists will have new means to choose (or avoid), modify and adapt treatments based on the individual genetic profile, ideally overcoming toxicity and resistance.

Authors Disclosure

The authors report no conflicts of interest in this work

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