The Basic Principals of Pharmacogenetics Testing in Cancer Treatment

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SUMMARY

Introduction: Precision medicine is an approach that considers genetics, environment and lifestyle factors when prevent and treat different diseases. The important part of precision medicine is pharmacogeneticss, a branch of clinical pharmacology that analyzes how genetic makeup affects the response to the drugs.

Methods: Since oncology is a field of particular interest in precision medicine, this article summarizes the basic principles of pharmacogenetics testing in cancer treatment.

Topic: The following topics have been discussed: Samples for pharmacogenetics testing (peripheral blood, tumor biopsy, liquid biopsy), methods in pharmacogenetics testing (conventional hotspot methods and comprehensive genome profiling), comprehensive genome profiling (CGP) in clinical settings and oncology therapy in Serbia that depends on genetic testing.

Conclusion: Pharmacogenetics testing provides the delivery of safe and efficient therapy. The usage of CGP methods opens up the possibility for the usage of therapies directed to genetic markers across tumor types. However, this approach needs evaluation through well-designed research projects and clinical trials.

Keywords: pharmacogenetics, polymerase chain reaction, next generation sequencing, comprehensive genome profiling

INTRODUCTION

The term „precision medicine" is relatively new, but the concept that takes into account genetic, environmental and lifestyle factors, has long been a part of therapeutic and preventive procedures [1]. Although precision medicine may be applied in different fields of medicine, oncology is of particular interest due to the increasing incidence of malignant diseases worldwide, high mortality rates and common usage of toxic and disfiguring therapies [2]. Increased knowledge about molecular pathways underlying cancer has begun to influence risk assessment, diagnostic classification' and therapeutic strategies years before

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Precision Medicine Initiative was announced. Among successful examples is the usage of imatinib, the tyrosine kinase inhibitor that revolutionized the treatment of patients with chronic myeloid leukemia (CML) (the inventors were awarded for „converting fatal cancer into a manageable condition" in 2009) [3]. It should be emphasized that CML patients are mandatorily tested for the presence of t(9;22) (Philadelphia chromosome) prior to imatinib administration. The introduction of polymerase chain reaction (PCR) - based methods into routine diagnostic practice enabled detection of BCR-ABL1 fusion gene transcript, quantification of residual disease during/after the therapy course, and detection of mutations related to imatinib resistance. The number of therapies tailored to specific genetic features has been continuously increasing and some of these therapies showed significant benefits. According to the last update, the US Food and Drug Administration (FDA) listed more than 150 drugs for the cancer treatment that contains information on genomic biomarkers in the labeling [4]. We are not so close to the moment when „matching a cancer cure to our genetics code is just as easy", but pharmacogenetics testing became the part of routine management in patients with breast, lung and colorectal cancers, as well as melanomas and hematologic malignancies. These tests play an important role in identifying potential responders, avoiding adverse events and optimizing drug dose.

METHODS

This article provides an overview of currently available pharmacogeneticss methods that are driving precision cancer treatment. The article addresses only biomarkers in drug labels analyzed by methods of cytogenetics or molecular genetic. Since the paper mainly discusses changes in individual genes, we prefer to use the term pharmacogeneticss over pharmacogenomics.

We searched PubMed, Google Scholar, SCIndex, Dimension, Scopus and Google for English and Serbian language abstracts, using the searching terms „pharmacogeneticss", „polymerase chain reaction", „next-generation sequencing", „comprehensive genome profiling", „precision medicine", „hotspots", „carcinoma", „cancer" and „cancer treatment". Based on expert selection review, we chose both open and blinded studies, reviews and meta-analysis, and available comments and editorials, related to the MESH terms.

TOPIC

Samples for pharmacogenetics testing

Pharmacogenetics biomarkers in the drug labels concern variations in the germline genome (germline variants) or somatic mutations.

The majority of cancer patients are treated with cytotoxic chemotherapy which is not targeted to specific mutations in tumor genome. However, variations in the toxicity and efficacy have been recorded between the patients, indicating that chemotherapy-induced phenotype is related to both somatic and hereditary (germline) variations. Pharmacogenetics analyses of germline variants commonly include single nucleotide polymorphisms (SNPs) in genes encoding drug metabolizing enzymes or drug transporters [5,6,7,8,9]. Well-known example includes thiopurine S-methyltransferase deficiency due to missense mutations in thiopurine S-methyltransferase (TPMT) gene. Treatment of acute lymphoblastic leukemia (ALL) with standard doses of mercaptopurine results in severe toxicity in patients with mutated TPMT. Both FDA and European Medicine Agency (EMA) recommend TPMT genotyping since patients with inactive alleles may be successfully treated with reduced doses of mercaptopurine [6]. Similarly, the usage of 5-fluorouracil (FU)/capecitabine leads to moderate or severe toxicity in up to 40% of patients as a result of low dihydropyrimidine dehydrogenase (DPD) activity. The majority of DPD deficient patients are carriers of mutations in DPYD, corresponding genes. Even though the association between DPYD genotypes and 5-FU/capecitabine efficacy has not been completely characterized, FDA and also The Netherlands National guideline for colorectal carcinoma recommends DPD and DPYD testing prior to treatment [10]. TPMT, DPYD, and other germline variants are commonly analyzed in peripheral blood samples. Since tumor samples represent a mixture of malignant and normal cells, they are unreliable in reflecting the germline genotype and should be avoided in germline analyses. In patients with hematological malignancies, saliva may be considered as a sample of choice [6].

GENE/MUTATION	DRUG	LABEL SECTION
TPMT	Cisplatin, Mercaptopurine, Thioguanine	Adverse reaction; Dosage and administration
DPYD	Capecitabine, Fluorouracil	Warnings and precautions
UGT1A1	Belinostat, Irinotecan	Dosage and administration
CYP2C9	Erdatifinib, Gefitinib	Use in specific populations; Adverse reactions
F II (Protrombin)	Tamoxifen	Warnings and precautions
F V (Leiden)	Tamoxifen	Warnings and precautions

Table 1. FDA recommendations for testing of germline mutations in cancer treatment

TPMT - thiopurine S-methyltransferase;
DPYD - Dihydropyrimidine Dehydrogenase;
UGT1A1 - UDP Glucuronosyltransferase Family 1 Member A1;
CYP2C9 - Cytochrome P450 2C9;
F II – Faktor II, Protrombin;
F V- Faktor V, Leiden.

Table 1 presents an overview of germline variants relevant to cancer treatment.

Differently to germline variants that commonly affect genes encoding drug-metabolizing enzymes and drug transporters, somatic mutations affect tumor suppressor genes, oncogenes or genes involved in DNA reparation, and usually represent „cancer drivers". Pharmacogenetics testing of somatic mutations is used to identify candidates for different targeted therapies and includes detection of base substitutions, nucleotide insertions/deletions, a variable number of (nucleotides) tandem repeats, (gene) copy number variations, chromosomal translocations, and altered gene expression. Cancer drivers may be targets for the development of both safer and more efficient therapies. So far, examples include the success of imatinib in Philadelphia chromosome-positive CML, trastuzumab in breast cancer with human epidermal growth factor receptor 2 (HER2) amplification, vemurafenib in B-Raf proto-oncogene (BRAF) - mutated melanoma, erlotinib in epidermal growth factor receptor (EGFR)-mutated non-

small cell lung cancer (NSCLC) and other [11, 12, 13]. Pharmacogenetics testing related to targeted therapy is performed on tumor tissue, commonly formalin-fixed paraffin-embedded (FFPE); in patients with leukemia, bone marrow aspirates/blood samples are analyzed. However, in some patients tumors are inaccessible or biopsy is contraindicated due to unfavorable clinical conditions. In recent years numerous research projects have been focused on circulating DNA derived from necrotic or apoptotic tumor cells (ctDNA). Analysis of ctDNA from serum/plasma („liquid biopsy") may be a powerful tool in pharmacogenetics because it reflects molecular heterogeneity and evolution over time of both, tumor and metastasis. EGFR testing demonstrated high concordance between tumor and liquid biopsies of NSCLC. The diagnostic value of ctDNA was also confirmed in colorectal cancer [14]. So far, FDA approved the use of gefitinib in NSCLC patients with EGFR mutations detected in ctDNA, but only when it's impossible to perform a tissue biopsy [15]. The examples of germline variants relevant for cancer treat-

GENE/MUTATION	DRUG	LABELING SECTION
BRAF	Dabrafenib, Trametinib, Vemurafenib	Indications and usage; Dosage and administration; Warnings and precautions, Adverse reactions; Clinical pharmacology
ALK	Lorlatinib	Indications and usage; Adverse reactions
ROS1	Entrectinib	Indications and usage; Dosage and administration; Adverse reactions; Use in specific populations; Clinical pharmacology
EGFR	Erlotinib, Gefitinib, Panitumumab	Indications and usage; Dosage and administration; Adverse reactions
Chromosome 17p	Ibrutinib	Indications and usage
BCL-ABL1	Imatinib, Nilotinib,	Indications and usage
FLT3	Midostaurin	Indications and usage; Dosage and administration; Adverse reactions
MSI	Nivolumab, Pembrolizumab	Indications and usage
BRCA	Olaparib, Talazoparib	Indications and usage; Dosage and administration; Warnings and precautions; Adverse reactions
KRAS	Cetuximab	Indications and usage

Table 2. Examples of mandatory testing for the presence of somatic mutations in respect to treatment with targeted therapy (FDA list)

BRAF - B-Raf proto-oncogene;
ALK - anaplastic lymphoma kinase;
ROS1 – C-ROS Proto-Oncogene 1;
EGFR - epidermal growth factor receptor;
FLT3 – FMS-like tyrosine kinase 3;
MSI - Microsatellite Instability;
BRCA - Breast Cancer Gene;
KRAS – Kirsten rat sarcoma viral oncogene homolog.

ment are presented in table 2.

Methods in pharmacogenetics testing

Pharmacogenetics biomarkers can be determined by cytogenetics, fluorescent *in situ* hibridization (FISH), a variety of polymerase chain reaction (PCR)-based methods, or by DNA sequencing.

Germline variants are commonly analyzed by Real-Time (RQ) PCR, PCR-RFLP (restriction fragment length polymorphism) or PCR-ARMS (allele refractory mutation system) [16, 17]. The majority of laboratories use in-house methods validated on regional/country population.

Detection of genetic variations in tumor cells employs a broader spectrum of methods. Regarding the number of analyzed markers, these methods can be divided into three distinct categories. The first category includes methods that analyze/detect one target. For example, RQ-PCR is used to detect BRAF V600E mutation in melanoma; reverse transcriptase (RT) PCR is used for detection and quantification of breakpoint cluster region-proto-oncogene tyrosine-protein kinase (BCR-ABL1) fusion gene transcript in CML; FISH is a gold standard for detection of Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) gene rearrangement in NSCLC, etc. Detection of somatic mutations in pharmacogenomic testing can be performed by in-house methods. However, the usage of CE marking IVD (*in vitro* diagnostic device) tests (devices complied with the European *in vitro* Diagnostic Devices Directive 98/79/EC) or FDA recommended tests is preferred [18].

The second category of methods includes next-generation sequencing (NGS) to detect the most frequent variations („hotspots") that occur in limited areas of genes of interest. Optimized NGS panels for a wide range of cancers (breast cancer, colorectal cancer, melanoma, lung cancer, glioma, prostate cancer, ovarian cancer, sarcoma) and hematological malignances (myeloid malignancies, chronic lymphocytic leukemia) are offered by companies, or laboratories can contact companies to create NGS panels that meet their requirements. The second category of methods also includes EndoPredict® (Myriad Genetics), a multigene test that combines the expression of cancer-related genes with con-

ventional prognostic factors (nodal status and tumor size) to predict the likelihood of disease progression/ metastases and thus guide treatment in ER+/Her2- early-stage breast cancer patients. The clinical value of EndoPredict® and similar tests (Oncotype DX™, MammaPrint®, Genomic Grade Index®, PAM50™, Breast Cancer Index™) was confirmed in practice (FDA approved) [19, 20].

Conventional hotspot methods that detect one or more variants in particular area(s) of the gene(s) are (and will be) important part of diagnostic and treatment procedures in patients with malignant diseases. However, these methods cannot address the increasing complexity of therapeutically relevant genomic and clinical information [21]. The third category of methods includes comprehensive genomic profiling (CGP), which is testing of all the known clinically relevant cancer genes for the most common classes of alterations. The CGP has already become an important procedure in the management of patients with cancer, as discussed in the text below. The list of FDA approved pharmacogenetics tests is available at http://www.fda.gov/companiondiagnostics.

Comprehensive genomic profiling

The main advantage of CGP over the hotspot testing is an analysis of the most common variants (base substitutions, insertions/deletions of nucleotides, gene rearrangements and copy number alterations) in all clinically relevant cancer genes in one run. Considering potential complications, scarce biopsy and frequent inability to repeat the procedure, the possibility of CGP in one assay became a valuable tool in oncology practice [22]. For that reason, guidelines for advanced/metastatic NSCLC recommend that molecular testing such as EGFR, anaplastic lymphoma kinase (ALK), C-ROS Proto-Oncogene 1 (ROS1), B-Raf proto-oncogene (BRAF) should be conducted as a part of broader molecular profiling. In addition, published data clearly imply lower sensitivity of conventional hotspot methods compared to CGP (e.g. 17% of EGFR exon 9 deletions are missed by hotspot testing, 35% of ALK rearrangements are missed by FISH, etc.) [23]. Thus, CGP detects gene alterations missed by hotspot testing and potentially converts „noncandidates" to „candidates" for targeted therapy. Of note, CGP detects both inherited and

acquired mutations in the tumor. However, the report of pharmacogenetics testing is intended for making a decision on therapy, not for counseling on hereditary cancer [24].

The well-known example of CGP test is FondationOne® Companion diagnostic (F1CDx) (Foundation Medicine Inc) that analyses the most common genetic aberrations in a total of 324 cancer-related genes in DNA from FFPE tumor tissue. The test also provides information on microsatellite instability (MSI) and tumor mutation burden (TMB), both relevant for the introduction of immunotherapy. To support clinical decision making, a report of F1CDx testing includes the genetic profile of tumors in association with approved therapies or options for clinical trials [25].

It should be emphasized that CGP improved our understanding of cancer as a complex disease of the genome and opened a possibility to classify (and treat) tumors according to biomarkers (mutations) across tissue/organ types.

Oncology therapy in Serbia that depends on genomic testing

Based on the list of medicines „B" and „C" prescribed by the Republic Health Insurance Fund of Serbia [26], prescribing of the particular drugs depends on genetic testing (Table 3). In Serbia, genetic testing is necessary for 13 drugs during the therapy in the patients with colorectal cancer, breast cancer, non-small cell lung cancer, and skin melanoma, chronic myeloid leukemia, as well as serous epithelial carcinoma of the ovary, fallopian tube, or primary peritoneal carcinoma.

CONCLUSION

Pharmacogenetics testing became a part of

DRUG	LABELING SECTION
trastuzumab (Herceptin®)	Breast cancer: HER-2 overexpression
cetuximab (Erbitux®)	Colorectal cancer: metastatic disease, exclusively for the patients with tumors containing the unmutated K/Ras gene; in the patients with wild-type RAS which have expressing epidermal growth factor receptors (EGFR)
panitumumab (Vectibix®)	Colorectal cancer: metastatic disease, exclusively for the patients with tumors containing the unmutated K/Ras gene; in the patients with wild-type RAS which have expressing epidermal growth factor receptors (EGFR)
pertuzumab (Perjeta®)	Breast cancer: patients with HER-2-positive cancer; metastatic HER-2-positive breast cancer
trastuzumab emtanzin (Kadcyla®)	Breast cancer: HER-2-positive cancer
gefitinib (Iressa®)	Non-small cell lung cancer in stage IIIb and IV: in the patients with a positive test for the tyrosine kinase mutation of the epidermal growth factor receptor (EGFR-TK)
erlotinib (Tarceva®, Inopran®, Erlotinib Actavis®)	Non-small cell lung cancer in stage IIIb and IV: in the patients with a positive test for the tyrosine kinase mutation of the epidermal growth factor receptor (EGFR-TK)
lapatinib (Tyverb®)	Breast cancer: metastatic HER-2-positive breast cancer
afatinib (Giotrif®)	Non-small cell lung cancer in stage IIIb and IV: in the patients with a positive test for the tyrosine kinase mutation of the epidermal growth factor receptor (EGFR-TK)
vemurafenib (Zelboraf®)	Skin melanoma: advanced and/or metastatic, BRAF positive, patients
olaparib (Lynparza®)	In patients with relapsing, platinum-sensitive, BRCA-mutated (germinative and/or somatic) serous epithelial carcinoma of the ovary, fallopian tube, or primarily peritoneal carcinoma, high grade, who have responded (complete or partial response) to chemotherapy based on platinum
paclitaxel (Paclitaxel Ebewe®, Paclitaxel Teva®, Sindaxel®, Pataxel®, Paclitaxel®)	Breast cancer: adjuvant chemotherapy for node negative disease, in case prognostic factors contribute to high risk for relapse (HER-2 3+)
imatinib (Alvotinib®, Imatinib Pharmaswiss®, Meaxin®, Imarem®, Plivatinib®, Glimatin®)	Chronic myeloid leukemia with Philadelphia chromosome and/or bcr-abl rearrangement

Table 3. Prescribing of the particular drugs depending on genetic testing in Serbia* [25]

*Segregate indications mentioning gene mutations as a prerequisite for receiving therapy;

HER-2 - human epidermal growth factor receptor 2; BRAF - B-Raf proto-oncogene; BRCA - Breast Cancer Gene; bcr-abl - breakpoint cluster region-proto-oncogene tyrosine-protein kinase.

routine clinical practice allowing delivery of safe and efficient therapy.

It's obvious that cancer treatment is undergoing a fundamental change moving toward the usage of targeted therapies for subsets of patients with certain molecular characteristics, across multiple tumor types. Diagnostic methods for comprehensive genetic profiling of tumors are essential for the successful delivery of personalized therapy. There is no doubt that decreasing costs will allow the broader application of CGP in clinical practice (initial evaluation in majority/all patients, assessment of clonal evolution during the therapy and at relapse). The concept of precision medicine is so appealing, but the usage of therapies directed to genetic markers across tumor types needs evaluation through well-designed research projects and clinical trials.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Osnovni principi farmakogenetičkog testiranja u onkologiji

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KRATAK SADRŽAJ

Uvod: Precizna medicina je pristup koji prilikom prevencije i lečenja bolesti uzima u obzir genetičke faktore, okruženje i način života. Važan deo precizne medicine je farmakogenetika, deo kliničke farmakologije koji se bavi uticajem genetičkih varijanti na odgovor na lek.

Metode: Pošto je onkologija među oblastima u kojima se najviše primenjuje pristup precizne medicine, ovaj članak daje pregled osnovnih principa farmakogenetičkog testiranja prilikom lečenja malignih bolesti.

Tema: U radu su razmatrane sledeće teme: uzorci za farmakogenetičko testiranje (periferna krv, biopsija tumora, tečna biopsija), metode koje se primenjuju u farmakogenetičkom testiranju (konvencionalne metode za analizu takozvanih „vrućih mesta" i sveobuhvatno profilisanje genoma), primena sveobuhvatnog profilisanja genoma u kliničkoj praksi i onkološka terapija u Srbiji za koju je neophodno genetičko testiranje.

Zaključak: Farmakogenetičko testiranje doprinosi primeni bezbedne i efikasne terapije. Primena CGP metoda dalje otvara mogućnost lečenja na osnovu genetičkim markera nezavisno od anatomskog tipa tumora. Međutim, ovaj pristup zahteva evaluaciju kroz dobro dizajnirana istraživanja i kliničke studije.

Ključne reči: farmakogenetika, *polymerase chain reaction*, sekvencioniranje naredne generacije, sveobuhvatno genomsko profilisanje