Introduction

Individual Biomarkers Using Molecular Personalized Medicine Approaches

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Personalized medicine · Genomics · Proteomics · Metabolomics · Targeted therapy

Abstract
Molecular personalized medicine tries to generate individual predictive biomarkers to assist doctors in their decision making. These are thought to improve the efficacy and lower the toxicity of a treatment. The molecular basis of the desired high-precision prediction is modern “omex” technologies providing high-throughput bioanalytical methods. These include genomics and epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, imaging, and functional analyses. In most cases, producing big data also requires a complex biomathematical analysis. Using molecular personalized medicine, the conventional physician’s check of biomarker results may no longer be sufficient. By contrast, the physician may need to cooperate with the biomathematician to achieve the desired prediction on the basis of the analysis of individual big data typically produced by omex technologies. Identification of individual biomarkers using molecular personalized medicine approaches is thought to allow a decision-making for the precise use of a targeted therapy, selecting the successful therapeutic tool from a panel of preexisting drugs or medical products. This should avoid the treatment of nonresponders and responders that produces intolerable unwanted effects.

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Introduction

One size does not fit all [1]: this may also be true for medical therapy including drug therapy. The efficacy of antidepressants is restricted to less than 40% of patients. Similar low efficacy rates apply to drugs for the treatment of asthma and diabetes. Even with cancer drugs, tumor control rate may be no higher than around 75%, contributing to inefficacy...
combined with toxicity in 25% of the patients. These facts paved the way for molecular personalized medicine trying to generate individual predictive markers for efficacy and toxicity of a treatment. The molecular basis of the desired high-precision prediction is modern "omex" technologies providing high-throughput bioanalytical methods. These include genomics and epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, imaging, and functional analyses. In most cases, producing big data also requires a complex biomathematical analysis. The conventional physician’s check of biomarker results is no longer sufficient; the physician needs to cooperate with the biomathematician to achieve the desired prediction on the basis of individual big data typically produced by omex technologies. A typical clinical application is the prediction of unwanted drug effects. An example may be vemurafenib, a BRAF inhibitor for the treatment of malignant melanomas that can produce spinaliomas. In some cases, RAS mutations are able to predict an existing individual risk of cutaneous carcinomas [2]. Another example is the prediction of the therapeutic response. Genetic variants may lead to alterations of metabolism or excretion of a drug. Recognition of these variants should allow for an adaptation of a drug’s dosage. This includes the prescription of statins to lower serum cholesterol concentration. Diagnostics of the gene variants of statin transport proteins allows recognizing a reduced hepatic admission influencing the drug’s efficacy [3]. Tamoxifen is a drug for a postoperative treatment of estrogen receptor-positive breast carcinomas, whose efficacy requires an enzymatic conversion of the drug. Ten percent of Caucasian females possess a CYP2D6 gene defect, resulting in a reduced drug efficacy [4]. This result may be strongly influenced by the gene source. For CYP2D6 genotyping, germ cells rather than tumor cells seem to be appropriate as a DNA source [5]. These examples may characterize the philosophy of individualized medicine, namely the broad application of omex-based prediction principles using (a) omex diagnostics, followed by (b) a mathematically based decision-making for (c) a precise use of a targeted therapy, selecting the successful therapeutic tool from (d) a panel of preexisting tools (drugs, medical products), and avoiding (e) the treatment of both nonresponders and (f) responders producing intolerable unwanted drug effects. A recent comprehensive review that was also used for the present publication has been published by Friedrich et al. [1].

**Materials and Methods**

A systematic search was carried out in PubMed (www.ncbi.nlm.nih.gov/pubmed), in the Cochrane Library (www.thecochranelibrary.com), and in the body of literature published by the National Academies of Sciences and/or Medicine of the UK, USA, and Germany. Defined search strategies and selection criteria were used to evaluate the different therapies. Keywords ("MeSH") were favored over words in the text body. If possible, the basis for presenting the level of evidence was the evidence classification of the Oxford Centre of Evidence-Based Medicine. Whenever available, randomized controlled trials (RCTs) were given preference for discussing therapeutic issues. Side effects were also included in the analysis, as well as statistical tests, evaluations, the accuracy of formulation, safety (report on adverse events according to CONSORT Extension for Harms, ICH E2, ICH E3), reproducibility (according to DIN ISO 5725), and a discussion of data from the literature.

**Results and Discussion**

Important targets in oncology are tyrosine kinases [6]. In part, tyrosine kinase genes are also called proto-oncogenes. They regulate the coordinated cell division and cellular life time. Genetic alterations may induce tyrosine kinase deformations being a molecular key mechanism of the transformation of normal cells into malignant cells [6]. Thus, tyrosine kinase
inhibitors (TKIs) may be useful tools for a targeted tumor therapy. As an example, the antibody trastuzumab (Herceptin) may be useful for the treatment of breast tumors carrying HER2 gene expression errors [7]. Imatinib inhibits a different tyrosine kinase, i.e., an ABL kinase with inhibitory effects for c-KIT and PDGFRA proteins. They are used for the treatment of specific cases of chronic leukemia resulting in a 90% tumor control rate up to 5 years [8]. The rare gastrointestinal stromal tumors may produce a biomarker consisting of mutations of 2 associated genes. In contrast to conventional chemotherapy with a 5% clinical response rate in biomarker-positive gastrointestinal stromal tumors, imatinib may increase the response rate up to 50% [9, 10]. In malignant mucosal melanomas, multiple gene sequencing (e.g., KIT, BRAF, and NRAS) may be instrumental to identify individual biomarkers for the application of imatinib and related TKIs for the treatment of c-KIT-mutated metastases [11, 12]. Vemurafenib is another TKI that may be applied in BRAF-V600E-mutated and BRAF-V600K-mutated malignant melanomas [13]. Erlotinib and gefitinib can be used in specific epidermal growth factor receptor (EGFR) mutation-positive bronchial carcinomas [14], because the tyrosine kinase part of the EGFR may be mutated in 10% of the Caucasian and in 30% of the Asian population [15]. In the presence of these tumor markers, tumor control rate may be increased to 90% accompanied by an increase in the survival time to 27 months [16–19]. Interestingly, efficacy may be enhanced by an additional FGFR (fibroblast growth factor receptor) by influencing the rate of apoptosis. Another important target is the EGFR. A monoclonal antibody (cetuximab) directed against EGFR may be used for the treatment of colon carcinomas, head and neck carcinomas, as well as spinocellular carcinomas. The basic prerequisite, however, is the presence of the untruncated receptor and of the wild-type EGFR/K-Ras protein (a G-protein, which is cross talking with the EGFR), which quite frequently is not the case [20–23]. Thus, the challenge consists in the identification of patients with truncated EGFR and mutated EGFR/K-Ras proteins as biomarkers to exclude these patients from an inappropriate antibody treatment [24]. As a result, treatment costs may be reduced because the expensive treatment may be restricted to the biomarker-selected patients. Hedgehog pathway proteins may be a further target. Sporadically, basal cell carcinomas may produce various mutations of the hedgehog pathway. This includes the specific hedgehog protein (encoded by the TCTH1 gene as a biomarker) and the smoothened protein (the relevant biomarker gene is the SMO gene) [25]. In the presence of mutations, a hedgehog protein inhibition using small molecules may be indicated [26–29]. Despite highly complex omex-dependent biomarker-based prediction methods, targeted tumor therapies may fail. This may be due to the known high tumor mutation rates resulting in a typical genetic heterogeneity. This heterogeneity may contribute to resistance formation during treatment with TKIs, for example. Second, mutations of the BCR-ABL genes in leukemia patients are used to explain imatinib resistance observed several years after successful continuous imatinib therapies. EGFR gene alterations [30] or spontaneous mutations of proto-oncogenes may also influence the therapeutic activity of gefitinib and erlotinib [31, 32]. Biomarker-based treatment individualization exists also for nononcological therapy. Recently, a transmembrane transport protein medication has been approved for the therapy of cystic fibrosis (which is recessively inherited) [33, 34]. Two M. Osler genes (HHT1 and HHT2) have been identified coding for the proteins endoglin and activin receptor-like kinase [35]. As biomarkers, they may be used to follow questions of shunts in the brain, lung, and liver. Targeted gene capture and next-generation sequencing technologies play an increasing role in sensorineural hearing loss [36]. They may support the indication for very early pediatric cochlear implants. In cases of a pediatric auditory neuropathy, the OTOF gene may be instrumental because OTOF encodes the hair cell protein otoferlin. In inner hair cells, otoferlin controls an ionic channel that plays a role in frequency coding [37]. OTOF gene analysis allows the separation of presynaptic from postsynaptic auditory neuropathy. The absence of OTOF expression suggests a presynaptic
problem, and thus functioning auditory nerve fibers allowing a desired early CI implantation during babies’ first months of life [37]. Widely used for early pediatric CI indication is the mutation analysis of connexin 26 [38, 39] whose absence or insufficient expression may lead to alterations of cochlear gap junctions [40]. Cochlear gap junctions play a role in the prohibition of a sensorineural hearing loss-inducing potassium intoxication of parts of the inner ear. Under development is the DFNA3 gene analysis, which encodes the ionic channel KCNQ4 in hair cells. KCNQ4 is a crucial channel required at the end of the mechanoelectrical transduction cycle [41]. Absence of KCNQ4 may result in deafness, and thus DFNA3 gene analysis may contribute to an early indication of pediatric cochlear implantation [42]. The same is true for Usher gene analyses [43] allowing an early indication of CI application to prepare for communication skills in cases of expected blind deafness [44]. Gene mutations of CYP1B1 and LTBP2 are associated with congenital glaucomas [45]; mutations of MYOC, OPTN, and WDR36 are associated with primary glaucomas, allowing genetic analyses to better predict disease probability [45, 46]. The genomics of neovascular retinal diseases, including the genes HTRA1 and ARMS2, may contribute to an early diagnosis. By simultaneously refraining from smoking and alcohol, early diagnosis may delay or even avoid age-dependent macular degeneration [47–49]. Furthermore, in cases with a CFH variant, first small studies revealed an increased odds ratio after application of the antibody ranibizumab [50]. Personalized medicine plays an important role in Leber congenital amaurosis. Identification of RPE56 determines the diagnosis. Moreover, animal experiments introducing the normal gene sequence into retinal ganglion cells and clinical trials provided convincing evidence of an effective gene therapy [51]. Furthermore, for cases of pediatric retinal degeneration with an RPE65 gene mutation, a genomics-based gene therapy has been developed. It resulted in an increase in the child’s quality of life [52, 53]. Using gene correction, a similar breakthrough in genomics-based gene therapy is expected for Duchenne muscular dystrophy [54–56]. Presently, genome analytical methods for application in ophthalmology are being further developed [57, 58].

Disclosure Statement

The author denies any conflict of interest that influences or biases his work.

References


