European Journal of Surgical Oncology xxx (2018) 1–6

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review

Host-dependent variables: The missing link to personalized medicine

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ARTICLE INFO

Article history:
Accepted 13 April 2018
Available online xxx

Keywords:
Cancer
Personalized medicine
Tumour microenvironment
Immunobiology
Targeted therapy
Pharmacogenetics

ABSTRACT

Individualized medicine has the potential to tailor anticancer therapy with the best response and highest safety margin to provide better patient care. However, modern targeted therapies are still being tested through clinical trials comparing preselected patient cohorts and assessed upon behaviour of group averages. Clinically manifesting malignant disease requires identification of host- and tumour-dependent variables such as biological characteristics of the tumour and its microenvironment including immune response features, and overall capacity of the host to receive, tolerate and efficiently utilize treatment. Contemporary medical oncology including clinical trial design need to refocus from assessing group averages to individuality taking into consideration time dependent host-associated characteristics and reinventing outliers to be appreciated as naturally occurring variables collectively determining the ultimate outcome of malignant disease.

Introduction

'*It is far more important to know what person the disease has than what disease the person has.*' Hippocrates 460–370 BC [1]

Despite significant advances in understanding cancer etiopathogenesis and the expanding tools available for earlier diagnosis, cancer treatment remains a challenging and complex task. The onset, clinical course and ultimate outcome of malignant disease is a time-dependent result of host/malignant cell interactions modulated by multimodal treatment [2]. The limited understanding of host/disease interactions substantially contributes to this challenge. In this review, we categorize issues with person-dependent characteristics in cancer treatment, address conceptual problems in their biological and medical understanding and discuss possible ways to overcome existing problems.

A clinically apparent disease is the result of interactions of a noxious substance (virus, bacteria, toxin, etc) with its host environment that, upon being challenged, mobilizes its internal armamentarium to attack the causative agent while taking advantage of external support such as treatment. Internal pathophysiological reactions against a noxious substance are of fundamental importance but may develop late or may lead to self-destruction of the host because of an exaggerated counterattack (such as anaphylaxis). The "clinically apparent disease" is thus always a result of *host/noxious element(s) interactions over a period of time*. Consequently, the same diagnosis may not result in the same clinical course in an individual patient. In parametric terms, personalization of therapy is to be considered at the host/patient level, such as germline genetic abnormalities leading to cancer syndromes, or genetic variations to identify potential drug intolerance and mishandling, often coined "pharmacogenetics", and host functional parameters such as immune capacity that can be therapeutically manipulated to enhance overall and sustainable patient anti-tumour response. This category also includes tissue events at the tumour/microenvironment interface such as angiogenesis and paracrine millieu

Abbreviations: SmPC (alias SPC), summary of product characteristics; IBD, inflammatory bowel disease; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cell-mediated cytotoxicity; APCs, antigen-presenting cells; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; GDPR, general data protection regulation.

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https://doi.org/10.1016/j.ejso.2018.04.014
0748-7983/

around malignant lesions that may differ for the primary and metastatic sites. The local level of inflammation, hypoxia and acidosis may substantially limit delivery of any active medicinal substance to the tumour lesion. Altogether, for any treatment to be successful it holds that it has to be tolerable by the host (pharmacokinetics and adverse "off-target" reactions), be deliverable in an active form to the target lesions to exert its intended effects (pharmacodynamics) and, once there, its bioavailable fraction must be capable of exerting the proposed direct or indirect target effects.

Gaps to be filled – the host matters

Currently, the most common vision of personalized medicine is that "the right drugs at the right doses are given to the right individual patient" [3], missing another conceptually important component – at the right time. This approach should be more effective and safer because the drug and dose are chosen according to a more-or-less meterologically parametric endpoint such as individual genomic fingerprints [4]. Facing clinically apparent malignant disease we need to identify both host-dependent and tumour-dependent variables ("all-in-one" approach), each of these playing significant and distinct roles during the clinical course of the disease. A definition of personalized medicine either as "targeted therapy" with tumour-dependent variables only, or as "targeted dosing" based on pharmacogenomics, is therefore an oversimplification of the concept of evolving and time dependent doctor/patient relationships [5]. In terms of personalized cancer medicine, it means that we do not treat the tumour but a specific individual with his/her tumour disease and comorbidities within a specified and often very pre-determined time window. Although this principle sounds trivial it goes back to and reinvents the original and today somewhat neglected but still fundamentally valid basic pharmacological postulates.

The tumour-dependent variables: predictive oncology and beyond

Tumour biomarkers are one of the most studied pathological parameters that include an array of cancer-associated genetic and/or protein-based determinants associated with disease promotion and progression have been described [6]. Cancer biomarkers, particular those associated with genetic mutations or epigenetic alterations, offer a *semiquantitative* way to identify individuals predisposed to particular types of cancers and can be useful in determining the aggressiveness of an identified cancer – prognostic biomarkers. Predictive biomarkers are useful in determining disease propensity of response to a given treatment [7]. Examples of such predictive biomarkers include *ERBB2* (HER2/neu) gene amplification, a marker indicating that breast cancer will likely respond to trastuzumab treatment [8], a mutation in exon 11 of *KIT* that encodes the proto-oncogene c-KIT, a marker indicating that a gastrointestinal stromal tumour will likely respond to imatinib treatment [9] and mutations in the tyrosine kinase domain of EGFR, a marker indicating that a patient's non-small-cell lung carcinoma will likely respond to gefitinib or erlotinib treatment [10].

It is important to consider the context of the tumour when selecting targeted therapies based on molecular genotyping. Different types of tumours may originate from different cellular types and are frequently driven by different combinations of genetic alterations. An effective treatment will probably require adaptive combinatorial treatment to counteract the cellular and molecular heterogeneity of cancer and to prevent or overcome drug resistance caused by clonal evolution [11]. In fact, it makes no sense to study obvious tumour heterogeneity if it will not to be used for possible treatment decision modifications related to new "actionable" mutations [12,13].

With emerging strategies to combat cancer with immunotherapies, immune-based predictive biomarkers are being studied in tumour tissues. Such an example is PD-L1 expression on tumour cells that is relevant also in stroma where M2 macrophages and cancer-associated fibroblast express PD-L1 and this feature contributes to the immunosuppressive power of the tumour [14].

Microenvironment context

The tumour microenvironment, local levels of inflammation, hypoxia and acidosis play significant roles in cancer development and tumour growth. Historically, the first link between inflammation and cancer was postulated in the mid-19th century, when German pathologist Rudolf Virchow described his discovery of leukocytes intermixed with tumour cells [15]. Decades of research have revealed that these pathophysiological processes can be utilized by cancer cells and subverted for tumour growth. It is becoming apparent that blocking chronic inflammation may play a role in cancer prevention and treatment in the future. Recent findings have shown that aspirin, taken for several years, reduces the long-term risk of some cancers, particularly colorectal cancer [16]. COX-independent mechanisms of aspirin pharmacological action such as inhibition of Wnt/β-catenin and NF-kB signaling and the acetylation of extra-COX proteins have been suggested to play a role in its chemopreventive effects but their practical relevance remains to be demonstrated in vivo at clinically achievable doses [17].

Host-dependent variables

While tumour biomarkers have been the subject of copious research, factors associated with host/patient millieu and timely context of treatment are less studied clinically and certainly are not considered in clinical practice.

Pharmacogenetics

The first important application of personalized therapy from host-related variables was the introduction of **pharmacogenetic principles.** Pharmacogenetic tools to individualize drug dosage are based on inherited factors being therefore particularly appealing for personalized anticancer treatment. These variations are often due to germline mutations in genes that encode drug-metabolizing enzymes or drug transporters. Although this concept is not new, the complexity of its clinical applicability remains a substantial barrier to its practical application.

Unfortunately, drug development and marketing authorization processes invariably dictate that the approved medicine is to be clinically used within its SmPC boundaries. Clinicians thus have no more involvement in exploring usage/toxicity issues further on in a given patient who may clinically present with drug-related symptoms. The only exceptions are pharmacovigilance principles that may suffer from underreporting unless severe or life-threatening episodes occur. This has led to underutilization of pharmacogenetic and therapeutic drug monitoring methods even in those clinical situations where they may have been clinically informative. This trend was recently somewhat reverted by new legislation on pharmacovigilance [18].

Some practical pharmacogenetic examples more or less applied in clinical practice include the chemotherapeutic drug 6-mercaptopurine, used in acute lymphoblastic leukaemia and IBD where dosing should be based upon thiopurine methyltransferase (TPMT) evaluation [19]. Similarly, irinotecan upfront dose reduction should be considered in patients homozygous for the variant form

Please cite this article in press as: Demlova R, et al., Host-dependent variables: The missing link to personalized medicine, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2018.04.014