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Mini Review Open Access

Functional Imaging in Cancer Drug Development: A Mini-Review

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Abstract

Cancer drug development is a lengthy and expensive process. Effective and non-invasive biomarkers are required to expedite the process of drug development. Functional imaging appears to have a rapidly emerging role, which is being discussed in this mini-review.

Keywords: Cancer drug development; Pharmacokinetic; Pharmacodynamics; FDA; Computerized tomography; Functional imaging

Introduction

Cancer drug development is a lengthy process; it can take as long as 15 years for a successful drug to reach to FDA (Food and Drug Administration) approval, going through all the different phases of pre-clinical and clinical research, ie, Phase I/II/III trials [1]. It has been previously estimated that out of 10,000 chemical compounds initially tested in pre-clinical studies, only 5 are eventually assessed in clinical trials, and only one achieves to gain official approval [2]. Furthermore, the final cost of the whole process until a drug reaches FDA approval has been approximately estimated to exceed $ 800,000,000 [3].

Cancer drug development starts with the identification of a relevant molecular target. Genetic instability as well as epigenetic changes is the driving force of tumorigenesis. Mutational activation of oncogenes or inactivation of tumor suppressor genes leads to malignant phenotypes. The expanding amount of our knowledge of cancer molecular biology has resulted in identifying several signal transduction pathways involved in cancer cell progression. Validation of the potential target is the essential next step to assess its biological significance in cancer, using e.g. RNA interference techniques or knockout animal models. High throughput screening of large chemical libraries is often the next step, aiming to identify a 'lead compound' with potential activity against the validated molecular target. Alternatively, rationally designing a compound to selectively fit the molecular target, based on crystallography structures, consists of another approach. Further modification of the chemical structure of the lead compound is often necessary to improve its pharmacokinetic and pharmacodynamic properties [2].

Defining the relevant Pharmacokinetic (PK) and Pharmacodynamic (PD) endpoints for each drug-candidate mandates repeated blood sampling, as well as tumour and normal tissue sampling. The need for the development of non-invasive techniques that will enable us to closely monitor what the body does to the drug and also, what the drug does to the body is becoming essential. Functional and molecular imaging techniques are constantly gaining recognition as useful non-invasive tools that can provide significant direct and indirect information regarding both PK and PD endpoints.

Conventional imaging with Computerized Tomography (CT), ultrasound scanning and magnetic resonance imaging (MRI) are widely used to measure the response to conventional cytotoxic chemotherapy, based on tumour size criteria. However, several of the newly discovered targeted molecular treatments demonstrate cytostatic, as opposed to the traditional cytotoxic effects of chemotherapy, therefore defining response by tumour shrinkage may be an inadequate way to measure efficacy.

Change in tumour vasculature has been incorporated in measuring response to anticancer treatments. Tissue perfusion has been previously estimated with the use of dynamic contrast CT [4]. Furthermore, changes in tumour tissue perfusion, vessel density and permeability have been measured with the use of dynamic contrast-enhanced MRI, following anti-cancer treatment [5]. Large molecular weight agents, such as ferric oxide particles covered in dextran have been used in clinical and pre-clinical research to measure blood volume, tumour vasculature and permeability [6]. Diffusion-weighted MRI has been previously used to monitor, as well as predict the response of rectal carcinoma to neo adjuvant chemo-radiotherapy [7]. Blood oxygenation level dependent MRI, utilizing the paramagnetic properties of deoxyhaemoglobin, can potentially provide significant information on tumour blood flow and vessel density [8]. Finally, Doppler ultrasound techniques, as well as combination with intravenous micro bubble contrast agents can provide useful information regarding tumour vasculature [9].

Magnetic resonance spectroscopy (MRS) can provide useful real-time in vivo PK properties when used to detect drugs containing nuclei with paramagnetic properties, e.g. 5-FU containing 19F [10]. Similarly, Positron Emission Tomography (PET) can provide PK data when used to detect drugs with radionuclide labels, e.g. temozolamide containing 11C [11]. These are excellent examples of non-invasive real time pharmacokinetic monitoring.

Several factors that can be used as PD endpoints, such as tissue bioenergetic status, tissue metabolism and phospholipid membrane turnover can be monitored with the use of MRS. Changes in the spectra of several metabolites (ie, adenosine triphosphate, choline, phosphanolamine, lactate, N-acetylaspartate), following anti-cancer treatment, can be potentially used to monitor response to treatment [12]. Similarly, PET can serve as another non-invasive technique through which significant information on several biologic factors acting as PD endpoints can be obtained, when positron-emitting reporter probes are exogenously administered; cellular proliferation of malignant tumours can be demonstrated with the use of thymidine containing 11C [13], tumour perfusion changes can be assessed with the use of H_2O

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molecules containing 15O [14], whereas fluorodeoxyglucose labeled with 18F has been previously utilized to demonstrate response of gastrointestinal stromal tumours to imatinib [15]. 2-(11C) thymidine PET has been successfully utilized in the case of a thymidylate synthase inhibitor study, where increased uptake of radiolabelled thymidine by the tumour provided evidence of thymidylate synthase inhibition and identified an alternative thymidine salvage pathway [16]. Finally, anti-HER2 antibodies radiolabelled with 124I have been previously used to detect over-expression of the HER2/neu gene, therefore potentially identifying patients suitable for treatment with Trastuzumab [17].

Angiogenesis consists of an important feature of malignant tissues through which oxygen supply is maintained for a constantly growing tumour mass, whereas cancer cells can also escape their primary site and metastasize to distant normal tissues. The established role of anti-angiogenic treatments in cancer, such as bevacizumab and sunitinib, delineates the significance of angiogenesis as a significant process to inhibit. Several efforts have been made to image in vivo tumour angiogenesis and its changes following treatment with anti-angiogenic factors; a humanized mouse monoclonal antibody against Vascular Endothelial Growth Factor (VEGF), HuMV833, was labeled with 124I and entered a phase I clinical trial, which demonstrated a fairly heterogeneous antibody distribution and clearance on PET imaging, in patients with advanced malignancies [18]. Similarly, Abegrin, a humanized monoclonal antibody against human integrin avβ3 (a recognized mediator of tumour angiogenesis) was conjugated with DOTA (dodecanetetraacetic acid) and labeled with 64Cu for PET imaging in tumour xenografts. The complex demonstrated very high specificity and uptake by integrin avβ3-positive tumours, which can be potentially utilized to characterize the PK properties of Abegrin and Abegrin –conjugates in clinical studies [19].

Furthermore, there is pre-clinical evidence that Gene expression imaging can potentially serve as an important PD endpoint; in vivo bioluminescent imaging of p53 gene expression post irradiation in a transgenic mouse model which expressed the luciferase gene upon activation by a p53-responsive promoter, confirmed an oscillatory pattern of p53 expression previously observed in cancer cell cultures [20]. Apoptosis is frequently observed upon treatment of cancer cells with either radiotherapy or chemotherapy. It can therefore consist of a potentially useful pharmacodynamic endpoint for anticancer treatments under investigation; annexin-V is a protein that specifically binds to phosphatidylserine residues on the surface of apoptotic cells. PET imaging of apoptosis with a derivative of annexin-V radiolabeled with 124I has shown promising activity [21]. Finally, multidrug-resistance is often attributed to the drug efflux transporter, P-glycoprotein (PgP). Evaluating PgP activity with non-invasive techniques can obviously provide very useful information on cancer drug resistance; both PET and SPECT (single photon emission computerized tomography) techniques have been utilized to measure PgP activity in vivo in human tumours [22].

MicroRNAs (miRNA) are single stranded, evolutionarily conserved non-coding RNAs of 19 to 25 nucleotides, coded by 3% in the human genome. They have been shown to regulate the expression of a variety of target genes that are involved in different cellular processes, which include cell proliferation, apoptosis, differentiation, stem cell development, and genes that are associated with various human diseases, including cancer. MicroRNAs exert their regulatory effect through direct interaction with mRNA, promoting its degradation or blocking translation initiation. So far, numerous microRNAs have been reported to play an oncogenic role by inhibiting tumor suppressor genes, and by controlling the genes which regulate cell cycle progression. MicroRNAs have also been reported to mediate metastasis by controlling genes that are responsible for epithelial–mesenchymal transition and cell invasion. After completion of target validation for several candidates, the development of therapeutic miRNAs is now moving to a new stage that involves pharmacological drug delivery, preclinical toxicology, and regulatory guidelines, using powerful molecular imaging techniques that can monitor processes inside the cell and study their complex pathways. Optical imaging methods have recently been developed to detect and monitor the functions of microRNAs in intact cells by noninvasively imaging them in living animals. The development of fluorescence-based reporter imaging strategies allowed for the monitoring of the functional status of miRNAs that were either endogenously expressed or transfected to be expressed. Functional in vivo miRNA imaging can potentially consist of a very specific pharmacodynamics biomarker for the future use of therapeutic miRNAs within the context of phase one clinical trials [23].

Advances in nanotechnology have permitted new possibilities for theranostics, which are defined as the combination of therapy and imaging within a single platform. The multi-functionality of nanoparticles enables the integration of imaging and therapy. Superparamagnetic Iron Oxide Nanoparticles (SPION) had emerged as an MRI contrast agent for tumor imaging due to their efficacy and safety. Recently, several chemical drugs, including paclitaxel, doxorubicin, and methotrexate have been combined with magnetic nanoparticles for cancer therapy, and preclinical data from xenograft models demonstrate tumour shrinkage, whereas the nanoparticle uptake was evaluated by in vivo MRI. Furthermore, nucleic acids are integrated into SPION, which protect them against enzymatic degradation and facilitate cellular internalization and endosomal release of molecules such as siRNAs. MRI-visible SPION have been found to carry a dual-modality function, facilitating caveolae-mediated endocytosis of SPION and cargo nucleic acid, and also monitoring of siRNA delivery to the target area [24].

In conclusion, the development of new targeted molecular treatments against cancer is a prolonged and very expensive process. Assessing PD properties within clinical trials cannot simply rely on tumour size measurements, as new treatments generally demonstrate cytostatic effects. Non-invasive functional evaluation of apoptosis, cellular proliferation, bioenergetic status, glucose utilization by cancer cells and changes in malignant tissue magnetic resonance spectra can serve as effective pharmacodynamic endpoints in modern cancer drug development, as tumour response based on the above features can potentially translate in clinical benefit. Functional imaging techniques focusing on pharmacokinetics monitoring, can provide real-time in vivo information without the need for repeated blood and tissue sampling. It is reasonable to expect that further optimization and standardization of functional imaging may reduce the cost of modern cancer drug development, as well as the time interval needed for a new anticancer treatment to demonstrate its potential efficacy and obtain regulatory approval.

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