ÜBERSICHTSARBEIT

Treatment planning in molecular radiotherapy

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Abstract

In molecular radiotherapy a radionuclide or a radioactively labelled pharmaceutical is administered to the patient. Treatment planning therefore comprises the determination of activity to administer. This administered activity should maximize tumour cell sterilization while minimizing normal tissue damage. In this work we present different approaches that are frequently used for determining the suitable activity. These approaches may be cohort- based as in chemotherapy, or patient-specific using dosimetry based on individual biokinetics. The approaches are different with respect to the input complexity, the corresponding costs and – in consequence – the quality of the therapy. In addition, a general scheme for data collection and analysis is proposed. To develop an effective and safe treatment, elaborate data need to be obtained. The main challenges, however, are collecting these complex data and analyse them properly.

Keywords: therapy planning, targeted radionuclide therapy, molecular radiotherapy, nuclear medicine, dosimetry

Therapieplanung in der molekularen Radiotherapie

Zusammenfassung

In der molekularen Radiotherapie wird dem Patienten ein Radionuklid oder ein radioaktiv markiertes Pharmazeutikum appliziert. Bei der Therapieplanung muss daher die zu applizierende Aktivität festgelegt werden. Diese soll die Tumorzellen unter Schonung des Normalgewebes vernichten.
In dieser Arbeit werden verschiedene häufig benutzte Methoden zur Bestimmung der am besten geeigneten Aktivität vorgestellt. Diese Verfahren können wie bei Chemotherapien kohortenbasiert sein, oder patientenspezifisch, beruhend auf der individuellen Biokinetik. Die Verfahren unterscheiden sich bezüglich der Komplexität der Eingabegrößen, bezüglich der Kosten und – als Konsequenz – der Qualität der Therapie. Zusätzlich wird ein verallgemeinertes Schema für die Datensammlung und -analyse vorgestellt. Voraussetzung für die Entwicklung einer effektiven und sicheren Behandlung ist es für die Therapieplanung ausreichend Daten zu gewinnen. Die entscheidenden Herausforderungen bestehen jedoch darin, diese komplexen Daten angemessen zu erheben und zu analysieren.

Schlüsselwörter: Therapieplannung, Radionuklidtherapie, Molekulare Radiotherapie, Nuklearmedizin, Dosimetrie

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1 Introduction

Molecular radiotherapy is, in most cases, a systemic or locoregional therapy, in which a radionuclide or a radioactively labelled pharmaceutical is administered to the patient. Therefore, treatment planning in nuclear medicine comprises the pre-therapeutic determination of the amount of activity to administer [1,2]. This administered activity should maximize tumour cell sterilization while minimizing normal tissue damage.

The therapeutic effect is mainly determined by the radiation absorbed doses and absorbed-dose rates to the patient's organs and tissues, which depend on the radionuclide chosen and the biokinetics of the radiopharmaceutical in the respective patient [3]. Consequently, treatment planning in molecular radiotherapy consists of choosing:

- the pharmaceutical, the appropriate radionuclide, the respective labelling process and its amount of substance,
- the activity to administer and,
- possibly, additional compounds to improve the biokinetics or the effect in the patient [4].

Additionally, the (relative) time points and durations of the different administrations of substances need being determined.

Another important determinant of therapy outcome is the absorbed dose-response relationship of the affected tumours and/or organs at risk. Therefore, when available, response models for deterministic effects should be used in treatment planning [2,5–7].

The purpose of this review on "Treatment Planning in Molecular Radiotherapy" is to provide recommendations to scientists and clinicians on how to plan the treatment of molecular radiotherapy using pre-therapeutic and/or peri-therapeutic clinical absorbed dose assessments. Various options for treatment planning in molecular radiotherapy are reviewed in the following section II. Based on the information in section II, in section III we propose a general scheme for the development of an adequate treatment planning method.

2 Methods for treatment planning

A list of options for determining the administered activity in molecular radiotherapy is given in Table 1. These methods differ with respect to the input complexity, corresponding costs and the quality of the obtained results [1]. Basically, the protocols for administering the radiopharmaceuticals may be assessed on a patient cohort basis (section II.A) [8], a standard approach in chemotherapy, or on a patient by patient basis (section II.B) using quantitative imaging methods [9,10] as in external beam radiotherapy [1,3,11]. In the latter case, the treatment planning may be based either on physical indexes (e.g. absorbed doses) or it additionally may take into account radiobiological parameters (thus leading to biologically effective doses, or equivalent) (section II.C) [12].

2.1 Cohort-based treatment planning

No elaborate treatment planning for the individual patient is performed in cohort-based treatment planning, as the activity to administer was determined in a preceding study. Items 1-3

Table 1
Options for the delivery of molecular radiotherapy (modified from [1]).

1. Fixed administered activity: single administration	Bone Pain Palliation Therapies	[17]
2. Fixed administered activity with multiple re-administrations dependent upon patient response according to defined indicators	Thyroid Cancer Treatment	[18]
3. Administered activity determined/constrained by rudimentary patient specific parameters such as body surface area, weight, target tissue mass, baseline platelet count etc.	^{90}Y ibritumomab tiuxetan	[14,19]
4. Administered activity determined by maximum absorbed dose allowable to a critical organ or its surrogate (e.g., red bone marrow, blood, kidney, whole body, lung) requiring knowledge of limited patient specific parameters (e.g. blood-based approach for thyroid cancer or radioimmunotherapy, kidney BED limit for radiopeptide therapy)	blood-based approach for thyroid cancer, kidney BED limit	[20,21]
5. Administered activity determined/constrained by more extensive patient specific parameters including biokinetics (e.g. effective half-life, percentage uptake, target tissue mass) and the desired absorbed dose to be delivered	Maxon Criterium for thyroid cancer	[22]
6. Administered activity determined through a higher level quantitative diagnostic work-up involving three-dimensional imaging and voxel-based model calculations specific to the patient	under development	[23]
7. Administered activity determined through a quantitative diagnostic work-up involving modelling, inclusion of radiobiological assessments and dosimetry specific to the patient.	under development	-
8. Administered activity and preload (of other pharmaceuticals to change biodistribution) determined through a quantitative diagnostic work-up involving modelling and biokinetics simulations followed by dosimetry specific to the patient.	^{90}Y-labelled anti-CD45 monoclonal antibody in acute myeloid leukemia treatment	[24,25]

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