EANM position paper: Theranostics in brain tumours, the present and the future

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ABSTRACT

Theranostics is an exciting field of nuclear medicine with proven efficacy in thyroid cancer, and more recently in neuro-endocrine tumours (NET) and prostate cancer. It is increasingly investigated in brain tumours, where there is substantial medical need for new therapeutic options. Existing concepts and theranostic pairs that are successfully employed in extra-cranial malignancies are being translated to the brain tumour setting. In parallel, new brain tumour-related theranostic targets are explored. So far, theranostic approaches show preliminary but encouraging results in cerebral malignancies. This paper provides the position of the EANM on the current stage, challenges, and opportunities on implementing theranostic concepts in neuro-oncology.

INTRODUCTION

Theranostic pairs have proven value in thyroid diseases, neuroendocrine tumours (NET) and prostate cancer (1,2). Recently, the Food and Drug Administration and the European Medicines Agency have approved [^{177}Lu]DOTATATE and [^{177}Lu]prostate specific membrane antigen (PSMA). Following this recent success in the care of NET and prostate cancer patients, there is increasing interest in theranostics in neuro-oncology.

Patients with brain tumours are often young, working and socially active with currently limited available therapies and dramatic poor outcomes. With the resulting desperate need for more effective therapy options, there is great hope for theranostics filling this gap for brain tumours. Radiation dose of such treatments are limited to tumoral tissue with preservation of healthy brain parenchyma. Specific molecular targets could realize a personalised treatment with pretherapeutic validation of target presence using the diagnostic ligand of a theranostic pair allowing an upfront prediction of response. Effectiveness could potentially be further increased by combination with current treatments such as external beam therapy or immunotherapy.

This paper states the position of the EANM on theranostics in meningiomas, gliomas, brain metastases and paediatric brain tumours.

THE CURRENT STATE OF THERANOSTICS IN MENINGIOMA

Meningiomas, representing 30% of primary intracranial tumours, are the intra-cranial tumours in which peptide receptor radionuclide therapy (PRRT) has most often been performed. Standard treatment options mainly encompass neurosurgical resection and external beam irradiation. PRRT is currently considered when these therapeutic options are exhausted (3,4). PRRT targets the somatostatin receptor (SSTR) type 2, which is invariably expressed in a very high concentration in meningiomas, and as well in well differentiated NET (5,6). Expression can be monitored with SSTR-targeting PET. Most of data on PRRT in meningiomas consist of retrospective studies of patients in the late course of the disease (3,7). Evidence gathered in prospective randomised controlled trials or in early disease stages is still lacking and urgently needed. However, the available data (8) seems promising – with disease control in 63% of patients, especially with Grade I and II tumours, which is impressive taking into consideration that the patients are often heavily pretreated. Potentially, application of PRRT in earlier disease stages may result in even higher stabilization rates. Moreover, identification of meningiomas with poorer prognosis (lesions with high glucose consumption and low SSTR expression) using dual-tracer imaging with pretherapeutic SSTR-PET and ^{18}F-FDG PET imaging (9) may help to stratify patients with regard to the predicted PRRT success. In addition, synchronous application of sequential external beam radiotherapy could boost efficiency (10).

THE CURRENT STATE OF THERANOSTICS IN OTHER INTRACRANIAL MALIGNANCIES

Gliomas

Gliomas are the most common malignant brain tumours and are characterized by a high level of treatment resistance, immune escape as well as temporospatial heterogeneity. Their

limited overall survival, in particular for patients with glioblastoma, underlines the need for new therapeutic concepts in the treatment of patients (11). A wide range of potential theranostic targets have been investigated in gliomas (tenascin, epidermal growth factor receptor, neurokinin type 1 receptor, SSTR, gastrin-releasing peptide receptor, L-type amino transporter 1 (LAT-1), carbonic anhydrase XII, PSMA, matrix metalloproteinase, DNA histone H1 complex, poly(ADP-ribose) polymerase 1, integrins, chemokine receptor 4, disialoganglioside and fibroblast activation protein), in varying settings and with variable, but mostly no encouraging, results (10,11). However, out of all these targets, amino-acids addressing LAT-1 are particularly interesting as they are transported across the blood-brain barrier (BBB) and are therefore also taken up in tumour with intact BBB (12). Both existing theranostic strategies and novel targets are currently under exploration (8,9). Innovative administration methods, such as radioembolization (combining radionuclide therapy and embolization), are also investigated (13).

Future studies should focus on identifying favourable theranostic target(s). As gliomas are characterized by large molecular heterogeneity, this could be achieved by transcriptome or multiplex immunohistochemistry. Regardless, the success of the so far tested theranostic approaches seems to partially be influenced by glioma size, type, grade, anatomical location, its extent of tumour cell invasion in the brain as well as time point of treatment during the course of the disease (14).

Brain metastases

As oncology care, in particular primary cancer control is advancing dramatically, brain metastases occur more frequently in many types of cancer. This leads to an increasing need

for more effective therapies. Current therapeutic options, consist of a combination of surgery, external radiotherapy, targeted and immune-modulating therapies (15).

A potential advantage of radionuclide therapy over immune therapy is that targeting can be directly reviewed using post-therapy PET/SPECT scanning (1,2), possibly leading to prediction of response and assessing heterogeneity within the patient.

Paediatric brain tumours

Paediatric central nervous system tumours remain the leading cause of cancer-related death in childhood and are, thus, in high need for improved treatment options. They differ in many aspects when compared to the disease in the adults, both in site and histology (16) . Only few studies have been published, mostly case series or safety studies combining innovative routes of administration with theranostics (17,18). More systematic research is, thus, clearly needed to investigate the potential role of theranostic concepts in paediatric brain tumours.

CHALLENGES IN NEURO-ONCOLOGIC TREATMENT

The main obstacle in treating brain as compared to extracerebral tumours is getting therapeutics over the BBB. This is despite some brain tumours and metastases disturbing the BBB integrity, and some producing a highly heterogeneous vasculature known as the blood tumour barrier (BTB) (19). The frequency and extent of BBB and BTB integrity alteration is heterogeneous between various brain tumour types, as shown by contrast enhancement on MRI (20). Several strategies are being developed to bypass the BBB/BTB (20–22): local administration (including intraventricular administration), convection-enhanced delivery (CED) for which a microcatheter is implanted into the tumour and hydraulic pressure is used to deliver the drugs into the tissue of interest, focused ultrasound (FUS) reshaping the

BBB/BTB using a targeted ultrasonic wave resulting in enhanced vessel permeability, and innovatively designed monoclonal antibodies and neural stem cells enabling passage through the BBB/BTB. These techniques are still under investigation and are complex and, as such, can only be performed in expert centres. Regardless, these innovative techniques should be further evaluated in clinical trials to determine the clinical effectiveness in the different brain tumour types and theranostic targets.

PERSPECTIVE OF THE EANM

As the need to improve brain tumour patient care is high, the potential for theranostics needs to be evaluated urgently. There the EANM would like to initiate a discussion and start considering to facilitate prospective trials together with other societies and stakeholders. Related regulatory aspects are rather heterogeneous across European countries, complicating large multicenter trials. Here, the member states of the EANM should support the harmonisation of the different regulations across the countries, which will facilitate collaborations. The policy and regulatory affairs committee is currently beside several other aspects also working on a central proposal, however the harmonization will have to be done actively by all members for each country.

Unmet needs and factors for success

With regard to the exciting potential of theranostics in brain malignancies, the EANM should help to define unmet needs in the operational, physics, and clinical fields. By working together, urgent issues along with those that are most likely to be factors for success can be identified. So far, PRRT is based on the standard approach for NET, i.e. a sequential treatment by multiple doses. This paradigm requires re-evaluation for intracranial malignancies, ideally including

personal tumoral dosimetry as well as alternative administration routes potentially boosting targeting (23). Moreover, as currently most PRRT studies in meningiomas used beta-emitters (^{177}Lu, ^{90}Y and ^{131}I), the efficiency of labelling with shorter range alpha-emitters should be investigated.

In general, synergistic approaches with external beam radiation or immunotherapy could potentially even be more effective than standalone therapy. Additionally, as with all theranostic approaches, the most optimal positioning in time (e.g. phase of treatment) and optimal target should be explored.

A major obstacle in moving this field forward so far has been the use of underpowered and uncontrolled clinical trial designs. The international community should, thus, strive towards sufficiently large and prospective randomized studies in order to generate high level-evidence on the efficacy of theranostic approaches in central nervous system tumours. Also, more basic and clinical research is necessary to define the added value of theranostics in brain tumours by defining novel targets, discovering mechanisms of action and guide dosing of theranostics in brain tumours.

Finally, efforts could also include the development of criteria for an appropriate use of radioligand therapy in neuro-oncology and recommendations to harmonize procedures which are highly variable across centres. A joint international procedure guideline is currently in preparation for PRRT in meningiomas and could serve as an example for other potential nuclear neuro-oncological therapy options

In conclusion, expanding the theranostic approach to intracranial malignancies is an exciting field of nuclear medicine. Precision medicine using a diagnostic-theranostic radionuclide pair could be the therapy approach of the (near) future: individual patients would receive a diagnostic PET/SPECT scan, preferably based on personalized targets through tissue

characterization. If adequate targeting is visualized, this could be followed by specific radionuclide therapy. Several clinical studies are on their way, but only if the international community works together towards large and prospective randomized studies, the future will show whether theranostic approaches will be able to serve as the desperately needed tools to improve patient care in neuro-oncology.

Declaration of interests

NLA has received honoraria for consultation or advisory board participation from Novartis and Telix and research funding from Novocure. AV has received honoraria for lectures from General Electrics, Curium and Eisai. HB received reader honoraria from Life Molecular Imaging, and dosing committee honoraria from Pharmtrace. IY receives speaker honoraria from Piramal and consultant fees from ABX-CRO and Blue Earth Diagnostics. IY receives research funding from the federal ministry of education and research Germany (grant number 031L0200B, PI, 2020-2022), German research foundation (grant number 491096247, PI, 2021-2024), international brain research organization (meeting support award 2022) and international society for cerebral blood flow and metabolism (satellite symposia sponsorship 2022).

SM was involved in advisory boards for Ely-Lilly and received speaker honoraria from GE Healthcare, Life Molecular Imaging, Novartis.

MB is supported by grants from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy – ID 390857198). MB received speaker honoraria from GE healthcare, Roche and LMI and is an advisor of LMI.

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