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Molecular imaging in lymphoma beyond ^{18}F -FDG-PET: understanding the biology and its implications for diagnostics and therapy

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Mature lymphoproliferative diseases are a heterogeneous group of neoplasms arising from different stages of B-cell and T-cell development. With improved understanding of the molecular processes in lymphoma and novel treatment options, arises a growing need for the molecular characterisation of tumours. Molecular imaging with single-photon-emission CT and PET using specific radionuclide tracers can provide whole-body information to investigate cancer biology, to evaluate phenotypic heterogeneity, to identify resistance to targeted therapy, and to assess the biodistribution of drugs in patients. In this Review, we evaluate the existing literature on molecular imaging in lymphoma, other than ^{18}F -fluorodeoxyglucose molecular imaging. The aim is to examine the contribution of molecular imaging to the understanding of the biology of lymphoma and to discuss potential implications for the diagnostics and therapy of this disease. Finally, we discuss possible applications for molecular imaging of patients with lymphoma in the clinical context.

Introduction

Lymphomas account for 3–4% of all malignancies worldwide. They arise from abnormal B lymphocytes, T lymphocytes, and natural killer cells at various stages of maturation, and are primarily classified as Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphoma is further subclassified into B-cell non-Hodgkin lymphoma and T-cell non-Hodgkin lymphoma, together accounting for more than 30 distinct subtypes with different diagnostic, prognostic, and therapeutic implications.¹ The definite diagnosis and molecular analysis of lymphoma relies predominantly on histopathological biopsies. However, because of the intrinsic heterogeneity of lymphoma, a single biopsy might not provide a complete characterisation of the lymphoma and the tumour microenvironment.

Clinical molecular imaging can provide phenotypic information of the entire tumour by non-invasively visualising and quantifying biological processes that are dysregulated in cancer.² The ability to characterise biological processes in vivo makes molecular imaging a valuable tool for visualising lymphoma biology and evaluating tumour heterogeneity, immune interactions, resistance patterns, and the biodistribution of drugs.² By providing crucial whole-body information, which is not obtainable through biopsies, molecular imaging could potentially improve patient management. Various modalities, such as single-photon-emission CT (SPECT), PET, MRI, magnetic resonance spectroscopy, optical imaging, and ultrasonography are applicable for molecular imaging. We focus on SPECT and PET imaging techniques because these modalities currently provide the most pragmatic solution for imaging of the whole body.

^{18}F -fluorodeoxyglucose (^{18}F -FDG) has become the most widely used molecular imaging tracer for routine diagnostic tests in patients with lymphoma, and its advantages and limitations are well documented. However, with the advent of targeted therapies, ^{18}F -FDG-PET cannot

be used to visualise tumour distribution of molecular targets at diagnosis and during therapy. Therefore, this Review will discuss molecular tracers other than ^{18}F -FDG in lymphomas.

The aim of this Review is to examine the contribution of molecular imaging to understanding the biology of lymphoma and its implications for treatment, thereby providing a framework for the future development of molecular tracers in the field of lymphoma imaging.

A brief history of molecular imaging in lymphoma

Several key developments have had an effect on the use of molecular imaging in lymphomas (figure 1). The Ann Arbor tumour staging system was introduced in 1971 for Hodgkin lymphoma and has since been adapted and used for most non-Hodgkin lymphomas. Around the same time, SPECT imaging with ^{67}Ga citrate was first studied as a tool for molecular imaging in lymphomas.³ In human plasma, Ga^{3+} is mostly bound to carrier proteins and iron transport molecules, such as transferrin, because of the similarity between Ga^{3+} and ferric ion (Fe^{3+}). The ability of ^{67}Ga to target tumours relies on the upregulation of transferrin receptors on the surface of tumour cells because of the iron dependent synthesis of deoxyribonucleotides required for DNA replication.⁴ The diagnostic performance of SPECT imaging, including ^{67}Ga citrate, was improved by combining CT with SPECT into a hybrid SPECT/CT modality in the early 1990s. However, important limitations of SPECT scanning with ^{67}Ga citrate include low specificity, low spatial resolution, and hepatic clearance, and have rendered this tracer obsolete in modern lymphoma testing.⁵

The next milestone for molecular imaging in lymphomas was the introduction of ^{18}F -FDG, a radiolabelled glucose analogue, for PET imaging in lymphomas, with the first associated study published in 1987. An

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Figure 1: Milestones in staging and response criteria, treatment, and molecular imaging in lymphoma, and molecular imaging in solid tumours. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. ^{18}F -FES= ^{18}F -fluoroestradiol. ^{18}F -FDG-PET= ^{18}F -fluorodeoxyglucose PET. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. SPECT=single-photon-emission CT.

Figure 2: Number of preclinical and clinical imaging studies in lymphoma. Counts are presented per year and categorised into different techniques. SPECT=single-photon-emission CT.

important characteristic of ^{18}F -FDG is the inability of cells to metabolise ^{18}F -FDG after phosphorylation, leading to intracellular trapping of the tracer. Compared with ^{67}Ga -SPECT, ^{18}F -FDG-PET has higher sensitivity, higher spatial and temporal resolution, and easier tracer uptake quantification.⁶ Despite limitations, such as reduced sensitivity in areas with high physiological glucose uptake, ^{18}F -FDG-PET/CT has become an integral part of lymphoma management. ^{18}F -FDG-PET/CT is

currently recommended for the staging and response assessment of lymphomas avid for ^{18}F -FDG, with the Lugano classification and Deauville criteria.⁷ In classical Hodgkin lymphoma, ^{18}F -FDG-PET/CT has allowed for response-guided treatment; however, clinical trials have not produced consistent results regarding interim response-guided treatment based on ^{18}F -FDG-PET/CT in non-Hodgkin lymphoma.⁸

In the research field, molecular imaging followed similar developmental milestones to those in clinical lymphoma imaging. Early molecular imaging studies almost exclusively relied on SPECT imaging, whereas studies from the late 1990s began to use SPECT/CT in conjunction with radioimmunotherapy (figure 2). From 2005 onwards, a steady increase in studies investigating PET tracers other than ^{18}F -FDG can be observed, and a corresponding decline of SPECT imaging-based studies occurs, illustrating increased interest and applications of PET in lymphomas.

Search results

We searched the online literature of PubMed, MEDLINE, and Embase for studies published between December, 1977, and April 16, 2019, with the search terms “lymphoma”, “lymphoid malignancy/malignancies”, “radioactive tracer/tracers”, “positron emission tomography”, “molecular imaging” and “single photon emission computed tomography” (see search strategy

and selection criteria panel for full information; appendix, p 1).

After elimination of duplicate articles, we initially identified 3014 publications. We excluded 2519 studies after manually screening the title and abstract, leaving 495 studies that were included for full text analysis. Another 189 studies were excluded after full text evaluation, resulting in 306 articles included for this Review (appendix, p 2).

Data from these 306 articles concerning year of publication, country where the research was done, PubMed ID, radionuclide used, imaging technique, tracer target, type of research (in vitro, in vivo [animal models], and in humans), and type of lymphoma were manually gathered and imported into R (version 3.5.1) for analysis and data visualisation using RStudio (version 1.0.153).

By synthesising these data, we identified 139 individual tracers with 50 distinct molecular and functional targets, that were labelled with 22 different radionuclides. A structured overview providing detailed information on the study type, tracers, and targets is provided (appendix, pp 4–9). Seven (2%) of 306 studies featured in-vitro experiments, 57 (19%) studies described preclinical in-vivo imaging, 22 (7%) studies combined in-vitro and in-vivo experiments, 219 (72%) studies were done in humans, and one study combined in-vitro and in-vivo experiments in animal and human models (<1%). B-cell lymphomas were most frequently studied, with 154 (50%) articles investigating B-cell non-Hodgkin lymphomas not otherwise specified, 59 (19%) articles studying aggressive B-cell non-Hodgkin lymphomas, 32 (11%) articles researching indolent B-cell non-Hodgkin lymphomas, and 18 (6%) articles investigating Hodgkin lymphomas. The T-cell non-Hodgkin lymphoma group comprised 19 (6%) studies, and 24 (8%) studies combined two or more of these lymphoma groups. Additionally, three ongoing trials were identified via ClinicalTrials.gov as of April 28, 2020 (appendix, p 10).

About half of all selected studies were done in the USA (145 [47%]). Other countries where molecular imaging in lymphoma research took place were Germany (28 [9%]), Italy (13 [4%]), the Netherlands (12 [4%]), Japan (11 [4%]), Taiwan (nine [3%]), and Australia (seven [2%]; appendix, p 3).

Targeting surface markers and biological processes

A total of 50 molecular targets for molecular imaging of lymphoma were identified following full text analysis (figure 3). The different targeting strategies for molecular imaging in lymphoma are visualised in figure 4. Seven targets were selected for detailed review on the basis of the number of publications or their potential clinical relevance: B-cell markers CD20 (MS4A1) and CD22, MHC class II molecule HLA-DR, apoptosis

Figure 4: Potential target groups with examples for molecular imaging applications in lymphoma
 ^{11}C -MET= ^{11}C -methionine. ^{18}F -FET= ^{18}F -fluoroethyltyrosine. ^{18}F -FLT= ^{18}F -fluorothymidine.

SPECT imaging for dosimetry of radioimmunotherapy. One study used the PET tracer ^{89}Zr -ibritumomab tiuxetan for dosimetry in seven patients with B-cell non-Hodgkin lymphoma.¹² Three studies were done without radioimmunotherapy to evaluate anti-CD20 tracer biodistribution.

PET-imaging studies investigating the tracer ^{89}Zr -rituximab provided important insights for the clinical application of CD20 imaging. ^{89}Zr -rituximab was initially investigated in five patients with indolent lymphomas who were scheduled to receive ^{90}Y -rituximab radioimmunotherapy.¹³ This study showed that preloading with unlabelled rituximab had a marked effect on tracer biodistribution, with less background and higher lymphoma lesion tracer uptake (higher tumour to background ratio) compared with no preloading with unlabelled rituximab. ^{89}Zr -rituximab was later investigated in six patients with relapsed or refractory diffuse large B-cell lymphoma, showing that tracer uptake (as quantified using standard uptake values) corresponded with CD20 expression measured via immunohistochemistry in tumour biopsies.¹⁴

Although no study specifically investigated the loss of CD20 expression after anti-CD20 immunotherapy, uptake of anti-CD20 tracers was observed in patients that

had previously received rituximab and relapsed after anti-CD20 therapy.^{13,14}

Three studies evaluated the CNS penetration of the anti-CD20 radioimmunotherapy compound ^{90}Y -ibritumomab tiuxetan, using SPECT imaging with ^{111}In -ibritumomab tiuxetan in 13 patients with relapsed or refractory primary CNS lymphoma.^{15–17} All studies reported low rates of tracer accumulation in CNS lymphoma lesions, responses restricted to these original tumour sites, and rapid progression in other CNS locations.^{15–17} The blood–brain barrier was hypothesised to be compromised at primary CNS lymphoma sites by extensive disease involvement, while preventing penetration of radioimmunotherapy compound in areas that later showed disease progression.^{15–17} Despite being limited by small cohorts, these findings were corroborated by a phase 3 trial (HOVON 105/ALLG NHL 24) in 2019,¹⁸ which showed no additional benefit of rituximab in patients given high dose methotrexate and cytarabine for primary CNS lymphoma.

These data validate the feasibility of imaging the biodistribution of CD20 antibodies in humans.¹⁴ However, important questions, such as the influence of different treatment regimens, B-cell lymphoma subtypes, B-cell depletion, and preload doses of unlabelled rituximab on

tracer uptake and clearance,¹³ should be answered before routine clinical use of CD20 imaging.

CD22

CD22, an immunoglobulin-like lectin that binds sialic acid, is exclusively expressed on B cells and involved in B-cell inhibition and interaction with T cells.¹⁹ From 16 studies ([5%] of 306) that investigated CD22, 12 were done by or in collaboration with one centre. More than half of the studies (nine of 16) focused on molecular imaging applications in antibody distribution, pharmacokinetics, and radiation dosimetry of radioimmunotherapy. In this context, the use of molecular imaging with different radionuclides allowed for evaluation of pharmacokinetic characteristics of monoclonal antibodies specific to CD22 in tumour tissue.^{20,21} Visualisation of physiological processes aided by molecular imaging and measurement of tumour-to-background ratios across different radio-immunoconjugates allowed for direct comparison of radioimmunotherapy compounds and more efficient treatment.^{21,22} Studies using PET and SPECT showed satisfactory tumour targeting with ⁶⁴Cu-labelled and ¹¹¹In-labelled tracers.^{23,24} Reported sensitivity of SPECT imaging on a lesion basis using ¹³¹I and ^{99m}Tc tracers ranged from 60% to 89%, however no specificity was reported. Clinical scans did not provide adequate spatial resolution and showed low tumour to background ratios in the spleen.²⁰ Since late 2013, the status of a planned phase 3 trial with the monoclonal antibody epratuzumab is still unknown (NCT00022685). In 2018, a phase 3 trial with the antibody-drug conjugate inotuzumab ozogamicin showed no added benefit for survival over the investigator's choice of treatment,²⁵ limiting the applicability for theragnostic imaging of CD22.

HLA-DR

18 studies (6%) imaged the MHC class II molecule HLA-DR. Loss of HLA-DR function by malignant cells allows them to escape immune surveillance and is associated with poor clinical outcomes.²⁶ Most of these studies (17 of 18) focused on applications of molecular imaging in the context of radioimmunotherapy. Molecular imaging was used to compare pharmacokinetics and biodistribution of various compounds, leading to the improvement of radioimmunotherapy.^{27,28} One study evaluated imaging of HLA-DR with ^{99m}Tc in a murine model,²⁹ and showed that ^{99m}Tc-anti-HLA-DR targeted HLA-DR positive cells. However, no studies were done in humans, in whom visualisation and quantification of HLA-DR expression and loss could be of prognostic value.²⁶

Apoptosis

16 studies (5%) reported imaging of apoptosis in lymphoma. Most tracers in these cases targeted the phospholipid phosphatidylserine, which is transported to the cell surface of apoptotic cells, where it is involved

in inducing phagocytosis via macrophages.³⁰ Several preclinical studies reported the ability of CASP-3 and CASP-7,³¹ La-antigen (SSB),³² and phosphatidylserine-specific SPECT and PET tracers to visualise the apoptotic response of tumour cells to radiation and chemotherapy.³³ In humans, the use of molecular imaging allowed visualisation of apoptosis induced by therapy,³⁴ predicted toxic effects in healthy tissue,³⁵ and associated early tracer uptake with a favourable response to treatment.³⁶ However, poor radiotracer biodistribution with high retention in the liver and intestines, and non-specific binding and tumour heterogeneity, limit the applicability of these tracers in molecular imaging of lymphoma.

CD37

Targets shared by both B-cell and T-cell lineages were observed in 14 (5%) studies. CD37 (reported in ten [3%] of 306 studies) is a glycosylated protein that is mostly expressed by mature B cells, and to a lesser extent by T cells, macrophages, monocytes, granulocytes, and dendritic cells. Although the biological function of CD37 is not completely understood, it is thought to be involved in prosurvival and proapoptotic signalling, recruitment, adhesion, chemotaxis, and transendothelial migration.³⁷ Studies investigating CD37 were limited to imaging with ¹¹¹In-labelled, ¹³¹I-labelled, and ¹⁷⁷Lu-labelled tracers, which were used for evaluating dosimetry and biodistribution of radioimmunotherapy compounds.^{38–40} Research focusing on molecular imaging of CD37 beyond radioimmunotherapy was scarce, with a small study reporting a lesion detection sensitivity of 40% using ¹³¹I-labelled anti-CD37 monoclonal antibodies.⁴¹ This suboptimal targeting performance might be explained by variable CD37 expression in diffuse large B-cell lymphoma.⁴² Further studies into CD37 as a target of radioimmunotherapy in non-Hodgkin lymphomas are underway (NCT01796171).

CD30

The tumour necrosis factor receptor CD30 (four studies [1%]) is expressed on activated T cells and a subgroup of B cells, where it plays an important role in cell survival and the crosstalk between T cells and B cells.⁴³ Brentuximab vedotin, an antibody-drug conjugate composed of the anti-CD30 monoclonal antibody brentuximab linked with monomethyl auristatin E (an antitubulin), has become a viable treatment option for patients with classical Hodgkin lymphoma and CD30-positive T-cell lymphomas.^{44,45} However, because not all patients respond to this treatment and responses to treatment can be variable, molecular imaging of CD30 might provide the necessary information to select appropriate treatment candidates. One murine study showed the high radiochemical yield, purity, and tumour specific activity of ⁸⁹Zr-labelled anti-CD30 monoclonal antibody.⁴⁶ With non-specific uptake of the tracer being small and high tumour to background tissue contrast,

^{89}Zr -labelled anti-CD30 monoclonal antibodies are a potential tool for analysing and managing patients receiving brentuximab vedotin.

CD5

Ten imaging studies (3%) investigated T-cell lineage markers, in particular CD5 (eight [3%] of 306 studies). CD5 is a type 1 transmembrane glycoprotein that is expressed by lymphoid precursor cells, T cells, and a small subset of mature B cells.⁴⁷ CD5-mediated signalling suppresses regulatory T cells,⁴⁸ and inhibits T-cell and B-cell receptor-mediated signalling.⁴⁷ CD5 has been exclusively investigated as a target for the imaging of cutaneous T-cell lymphoma with ^{111}In or ^{131}I radionuclides. Studies using ^{111}In showed CD5-specific binding of the tracer to both cutaneous and systemic lesions in patients with cutaneous T-cell lymphoma.⁴⁹ Although CD5 is an attractive target for clinical imaging of T cells, T-cell non-Hodgkin lymphomas, and CD5-targeted therapy, the development of novel tracers, specifically for PET imaging, is required before CD5 attains clinical usefulness.

Ongoing clinical imaging studies

There are three non- ^{18}F -FDG molecular imaging studies in lymphoma registered on ClinicalTrials.gov (appendix, p 10). One study is imaging CXCR4 with the ^{68}Ga -labelled agonist pentixafor with the aim of improving diagnosis and pretherapeutic evaluation (NCT03436342). Our own group is studying the use of ^{89}Zr -atezolizumab for evaluating PD-L1 expression in patients with diffuse large B-cell lymphoma (NCT03850028). The third trial aims at overcoming the diagnostic limitations in identifying primary CNS lymphoma with MRI by using the amino acid analogue ^{18}F -fluciclovine and ^{18}F -FDG with integrated PET/MRI scans (NCT03788354).

Summary of the status quo

The production of stable tracers with high yield and high specific activity for selected targets is feasible. The application of molecular imaging was predominantly investigated in the context of radioimmunotherapy for pharmacokinetics, radiation dosimetry, and prediction of off-target effects with SPECT based tracers. Although PET is clinically superior to SPECT, development of PET techniques over the past 50 years has been challenging because of the great investment and specialised knowledge required. Since the late 1980s, 106 studies have reported the use of SPECT/CT in 31 different radioimmunotherapy compounds (appendix, pp 11–12). These studies allowed direct comparison between radio-immunoconjugates, and selection of compounds with more favourable tumour-specific radiation. Nevertheless, the clinical application of radioimmunotherapy is limited. Some explanations might include high myelotoxicity associated with radioimmunotherapy treatments, the establishment of rituximab therapy, and reluctance

on the part of haematologists to use this novel and unconventional form of radiation therapy.

Outside the field of radioimmunotherapy, attempts to use molecular imaging to improve existing targeted treatments in lymphoma are limited to a few studies targeting CD20 (figure 1). Consequently, molecular imaging has not played a role in the development of novel targeted therapies for lymphoma to date. So far, studies evaluating the role of molecular imaging have been done in small and heterogeneous study populations. Additionally, most radionuclides were only investigated using SPECT, resulting in lower specificity and spatial resolution when compared with clinical PET cameras. Regarding innovative immunotherapeutic options, such as immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy for lymphomas, we only identified one preclinical study in lymphoma that used multimodal imaging techniques to track genetically engineered T cells.⁵⁰ Preclinical studies have mostly evaluated molecular imaging in the context of tracer development, rather than exploring new biological rationales or clinically relevant biological questions. This finding might be explained by the availability of practical and inexpensive techniques for visualisation and investigation of molecular processes such as immunofluorescence, optical imaging, flow cytometry, and immunohistochemistry in the preclinical setting. However, these techniques often cannot be used for in-vivo imaging and clinical applications.

The limited effect of molecular imaging with tracers other than ^{18}F -FDG in lymphomas is contrasted by developments in the field of solid oncology. Novel immunotherapeutic drugs have been used to produce tracers for molecular imaging in solid cancers to facilitate drug development;⁵¹ to improve diagnosis;⁵² to visualise biodistribution to predict toxic effects, off-target effects, and heterogeneity;⁵³ to evaluate drug combinations and dosimetry;^{54,55} to identify candidates for specific therapies;⁵⁶ and to predict target specific response (figure 1).⁵⁷

Future perspectives

The development of novel molecular imaging tracers is a complex process requiring advanced multidisciplinary knowledge. Other challenges include the high costs of tracer development with good manufacturing practice requirements and PET imaging, little awareness in stakeholders or investors, a complicated reimbursement process for novel imaging techniques, and practical issues, such as difficult accrual of patients in imaging trials without treatment. The promotion of dedicated multidisciplinary research teams, sharing of resources and data between specialties, novel funding strategies, collaboration with the industry, and effective study design are necessary for future molecular imaging efforts.⁵⁸ For a detailed discussion of the obstacles to clinical molecular imaging research and suggestions for distinct measures on how to overcome them, we refer readers to an excellent review on this topic.⁵⁸

Many of the potential applications of molecular imaging could be of importance within the context of personalised medicine. In oncology and haematology, the trend towards highly sophisticated therapies, which are dependent on the genetic and phenotypic makeup of the tumour cells, presents opportunities for molecular imaging in medical decision making. In time, molecular imaging might become more cost-effective by enabling the selection of treatment candidates for expensive targeted therapies.

Certain existing tracers represent future opportunities for molecular imaging in lymphomas. CXCR4, a chemokine receptor that is frequently overexpressed in haematological malignancies, has been visualised using different SPECT and PET tracers in the lymphoma setting. CXCR4 expression has been linked to prognosis in several

different lymphoma subtypes and preclinical research suggests a therapeutic synergy with rituximab.⁵⁹ Although clinical application of drugs that target CXCR4 is currently restricted to haematopoietic stem-cell transplantation, the therapeutic potential and the current development of tracers targeting CXCR4 for molecular imaging make it an intriguing candidate for future investigations. Novel tracers that are fibroblast activation protein (FAP) inhibitor based, which target tumour-associated fibroblasts, are candidates for general diagnostic imaging and might complement ¹⁸F-FDG-PET imaging, especially in indolent lymphoma subtypes.⁶⁰

One application for molecular imaging is during the early phase of drug development. In the field of immunotherapy, various novel compounds and treatment

Target		Known efficacy in lymphoma	Phase of development and clinical trial registry numbers
Immune checkpoint inhibitors*			
Atezolizumab	PD-L1	15% ORR (10% CR) with obinutuzumab in relapsed or refractory B-cell non-Hodgkin lymphoma; 88% ORR (78% CR) with R-CHOP in untreated diffuse large B-cell lymphoma	Phase 1, 2016 interim analysis (NCT02220842); phase 1b-2, interim analysis (NCT02596971)
Nivolumab	PD-1	Approved for relapsed or refractory classical Hodgkin lymphoma; hope for combination therapy, maintenance, or consolidation in non-Hodgkin lymphoma	Approved by FDA and EMA in 2016
Pembrolizumab	PD-1	Approved for relapsed or refractory classical Hodgkin lymphoma; hope for combination therapy, maintenance, or consolidation in non-Hodgkin lymphoma	Approved by FDA and EMA in 2017
Chimeric antigen receptor T-cell therapy†			
Axicabtagene ciloleucel	CD19	82% ORR (54% CR) in diffuse large B-cell lymphoma	Phase 2 (NCT02348216)
Tisagenlecleucel	CD19	52% ORR (40% CR) in diffuse large B-cell lymphoma	Phase 2 (NCT02445248)
Bispecific antibodies‡			
AFM13	CD30 and CD16	For relapsed or refractory classical Hodgkin lymphoma	Phase 2 (NCT02321592)
Blinatumomab	CD19 and CD3	43% ORR (19% CR) in B-cell non-Hodgkin lymphoma	Phase 2 study completed ⁶¹
Mosunetuzumab	CD20 and CD3	41% ORR (27% CR) in B-cell non-Hodgkin lymphoma	Phase 1, interim analysis completed ⁶²
RG6026	CD20 and CD3	For relapsed or refractory B-cell non-Hodgkin lymphoma; for relapsed or refractory B-cell non-Hodgkin lymphoma and untreated diffuse large B-cell lymphoma	Phase 1 (NCT03075696, NCT03533283); phase 1 (NCT03467373)
REGN1979	CD20 and CD3	For relapsed or refractory follicular lymphoma	Phase 2 (NCT03888105)
Antibody-drug conjugates§			
Brentuximab vedotin	CD30	Approved by FDA (for stages III and IV) and EMA (for stage IV) in 2018 for first-line therapy in classical Hodgkin lymphoma; not effective in primary mediastinal large B-cell lymphoma; 44% ORR (17% CR) in CD30-positive diffuse large B-cell lymphoma	Phase 2 study completed; ⁴⁴ phase 2 trial terminated; ⁶³ phase 2 study ⁶⁴
Camidanlumab tesirine	CD25	For relapsed or refractory classical Hodgkin lymphoma and non-Hodgkin lymphoma	Phase 1 (NCT02432235)
Loncastuximab tesirine	CD19	57% ORR (34% CR) in diffuse large B-cell lymphoma	Phase 1 study completed ⁶⁵
Naratuximab emtansine	CD37	For relapsed or refractory B-cell non-Hodgkin lymphoma	Phase 2 (NCT02564744)
Polatuzumab vedotin	CD79b	54% ORR (21% CR) with rituximab in diffuse large B-cell lymphoma	Phase 2 study completed ⁶⁶

ORR=objective response rate. CR=complete remission. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. FDA=US Food and Drug Administration. EMA=European Medicines Agency. *Specific applications of molecular imaging include correlating tracer uptake with response (investigating whether the effect is mediated through targeting the tumour microenvironment) and impact of standard therapy on PD-1 or PD-L1 expression in non-Hodgkin lymphoma.

†Specific applications include monitoring targeting ability and persistence of chimeric antigen receptor T cells in vivo (cell tracking) and identifying loss of the CD19 target.⁶⁷

‡Specific applications include monitoring CD19 expression over time, identifying loss of CD19 and early CD19-negative relapse, and confirming mechanism of action (separate tumour and effector cell visualisation). §Specific applications include identifying resistance (loss of CD30 in anaplastic large cell lymphoma), pinpointing biological differences in tracer uptake between lymphoma subtypes (no effect of brentuximab vedotin in primary mediastinal large B-cell lymphoma⁶⁸), selecting treatment candidates (eg, CD30-positive diffuse large B-cell lymphoma), investigating the effect of combination with other drugs (eg, immune checkpoint inhibitors) on tracer uptake, and examining the potential effect of anti-CD20 therapy on CD79b expression.

Table: Candidate drug groups and specific compounds for potential molecular imaging applications in lymphoma

modalities are being investigated, including intriguing candidates for clinical applications of molecular imaging (table). Valuable information could be provided by future molecular imaging, including insights into the biodistribution of the molecular target (important in case of tumour heterogeneity or unexpected off-target effects), and molecular target expression over time (important for understanding the effects of standard therapy and resistance to targeted therapy). Additionally, future molecular imaging could allow selection of treatment candidates on an individual level, prediction of response to targeted therapy, dosimetry (determination of an effective and safe dose), and pathophysiology (eg, correlating immunohistochemical target expression and clinical response with tracer uptake).

Immune checkpoint inhibitors are an important group of candidate drugs for molecular imaging. Monoclonal antibodies targeting PD-1, PD-L1, PD-L2, CTLA4, and CD47 have shown efficacy in patients with different lymphoma subtypes.^{68,69} For the treatment of advanced stage classical Hodgkin lymphoma, nivolumab was approved in 2016 and pembrolizumab was approved in 2017 (PD-1 checkpoint inhibitors). Although not effective as monotherapy in non-Hodgkin lymphoma, immune checkpoint inhibitors might still hold potential as part of combined treatment regimens.⁷⁰ PET imaging of the ⁸⁹Zr-labelled, PD-L1 checkpoint inhibitor, atezolizumab has been successfully done in a mixed cohort of 22 patients with bladder cancer, non-small cell lung carcinoma, and triple negative breast cancer.⁵⁷ These results suggest the feasibility and prognostic value of in-vivo imaging of tumour phenotypes in humans, and show the superiority of whole tumour characterisation with imaging over immunohistochemistry in histological biopsies from single sites. Nevertheless, further research and development is needed to validate these findings in bigger cohorts, acquire more safety data, and address issues such as cost-effectiveness.

Bispecific T-cell engagers and dual affinity retargeting compounds are another group of novel drugs relevant for molecular tracer development. Both formats of bispecific antibodies aim to directly link cytotoxic T cells to tumour cells, thereby increasing their antitumour activity. By labelling these bispecific antibodies and separately targeting T-cell and tumour cell markers, the proposed mechanism of action and potential off-target sites could be visualised in vivo. A study in patients with gastrointestinal adenocarcinoma used a radiolabelled bispecific T-cell engager targeting CD3 and CEA (CEACAM5) for molecular imaging, and described both heterogeneous tracer uptake in tumour lesions and signal accumulation in the lymphoid compartment.⁵³ These results show how the binding affinity of the different arms of such bispecific antibodies can affect biodistribution.⁵³ The bispecific, tetravalent chimeric antibody construct AFM13, which targets both CD30 and CD16a (FCGR3A), is being evaluated in a phase 2 trial (NCT02321592) after

showing a disease control rate of 61·5% in a phase 1b trial in patients with relapsed or refractory classical Hodgkin lymphoma.⁷¹ For the bispecific T-cell engagers blinatumomab (targeting CD19 and CD3) and mosunetuzumab (targeting CD20 and CD3), which have both shown activity in non-Hodgkin lymphoma,^{61,62} molecular imaging might provide information on target biodistribution, off-target effects, and potential heterogeneity.

The group of antibody-drug conjugates is being extensively studied for therapy in lymphomas.⁷² The anti-CD30 compound brentuximab vedotin was evaluated for integration into first-line treatment of patients with high-risk classical Hodgkin lymphoma, showing a more favourable toxicity profile than standard therapy, with equal efficacy.⁴⁴ Meanwhile, novel compounds such as the anti-CD25 antibody-drug conjugate camidanlumab tesirine (ADCT-301) are entering clinical testing in classical Hodgkin lymphoma (NCT02432235). Encouraging results in the setting of diffuse large B-cell lymphoma have been reported for the anti-CD79b antibody-drug conjugate polatuzumab vedotin,⁶⁶ the anti-CD19 antibody-drug conjugate loncastuximab tesirine,⁶⁵ and the anti-CD37 antibody-drug conjugate naratuximab emtansine (NCT02564744). By radiolabelling the monoclonal antibody portion of an antibody-drug conjugate, the biodistribution of its target could be visualised. As discussed in earlier sections, studies have shown the feasibility of imaging targets like CD30 and CD37. However, tracers based on the naked antibody portion of the respective antibody-drug conjugate should be developed to be able to draw meaningful conclusions from molecular imaging studies.

Another area for future molecular imaging in lymphoma is the tracking of chimeric antigen receptor T cells. Important preclinical work to image chimeric antigen receptor T-cell trafficking in models of solid malignancies was reported in 2020.⁷³ Until now, molecular imaging of chimeric antigen receptor T-cell therapy in humans has been reported in only seven patients with glioma.^{74,75} By using a ¹⁸F-labelled analogue of penciclovir, which is used in the treatment of herpes, researchers visualised the spatial expression of the herpes virus thymidine kinase reporter gene in CD8-positive cytotoxic T lymphocytes that were directly administered to the ventricular system for cellular therapy of patients with high-grade gliomas.⁷⁴ Early trials are underway to investigate imaging of cellular immunotherapy in lymphoma.^{50,76} In 2019, a preclinical study was able to visualise the concentration of PSMA (FOLH1) transduced chimeric antigen receptor T-cell xenograft models of acute lymphoblastic leukaemia (Nalm6 cell line) via serial PET scanning with the PSMA-specific tracer 2-(3-[1-carboxy-5-[(6-[¹⁸F]fluoropyridine-3-carbonyl)amino]pentyl]ureido)pentanedioic acid.⁷⁷ By visualising the biodistribution of chimeric antigen receptor T cells, molecular imaging could provide valuable insights in targeting lymphoma lesions. Furthermore,

Search strategy and selection criteria

We searched the online literature of PubMed, MEDLINE, and Embase with the search terms “lymphoma”, “lymphoid malignancy/malignancies”, “radioactive tracer/tracers”, “positron emission tomography”, “molecular imaging” and “single photon emission computed tomography” (for the full search terms see appendix, p 1). Studies published from December, 1977, to April 16, 2019, were included. Only articles in English were considered. Original articles concerning any applicability of molecular imaging in the management of lymphoma were incorporated. These articles encompassed in vitro, in vivo, and clinical studies. Radioimmunotherapy studies that used molecular imaging for dosimetry and planning of therapy were included. Studies using the PET tracer ^{18}F -FDG were excluded. Articles exclusively evaluating radioimmunotherapy were excluded. Duplicates were eliminated using Mendeley Desktop (version 1.1710; Elsevier, Amsterdam, Netherlands). The remaining articles were manually screened for title and abstract. Ongoing trials were consulted via ClinicalTrials.gov by combining the search terms “lymphoma” and “molecular imaging” with subsequent manual selection.

molecular imaging of the CD19 target of chimeric antigen receptor T cells might be used to monitor patients for loss of CD19, a major resistance mechanism in patients receiving this type of treatment.⁶⁷

Conclusion

Whether there will be a role for radionuclide tracers other than ^{18}F -FDG-PET in routine clinical diagnostics is unknown. Research suggests that molecular imaging is suited for patient and therapy tailored imaging in highly specific disease entities and patient cohorts, like in lymphoma. The target-specific information that can be obtained by molecular imaging becomes increasingly important in the context of immunotherapy and personalised medicine. Labelling of novel therapeutic compounds and imaging is feasible in patients with lymphoma. However, molecular imaging of lymphomas, outside the well developed field of radioimmunotherapy, has not been used to its full potential. Most studies in humans used SPECT imaging for radioimmunotherapy based on small cohorts of patients and were done by a small number of research groups.

Improved study design and collaborations and coordination between different specialties and with the industry are necessary to effectively implement what the scientific community has learned from this research for future molecular imaging applications. In particular, the integration of molecular imaging efforts with drug development is essential. Building awareness for the potential opportunities and applications of molecular imaging in lymphoma is required before its full clinical utility can be realised.

Contributors

XUK and FMMdJ searched the literature and manually selected articles. XUK also analysed and visualised the acquired data. AWJMG, WN, and TCK contributed to conceptualisation and writing of this Review with a focus on nuclear medicine and molecular imaging. MNL-dH and AJ-S contributed to conceptualisation and writing of this manuscript with a focus on pharmacology. WJP and TvM contributed to conceptualisation and writing of this Review with a focus on clinical and experimental haematology. AvdB and AD contributed to conceptualisation and writing of this Review with a focus on pathophysiology and biology. EGEV and MN developed the concept and design of this Review and acted as main supervisors. All authors contributed to writing and internal revision of the manuscript and approve of the review for submission.

Declaration of interests

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