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Workshop outcome and recommendations

Current use and future needs of radiopharmaceuticals labelled with radionuclides produced in reactors and possible alternatives

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1. BACKGROUND INFORMATION

1.1. Introduction

In August 2008, the Dutch Authorities made the European Medicines Agency aware of potential shortages of radiopharmaceuticals due to the temporary shutdown of the High Flux Reactor (HFR) in Petten by the Nuclear Authority in the Netherlands. The HFR in Petten is responsible for the production of a large percentage of all radionuclides used as part of radiopharmaceutical medicinal products in Europe and about one third of the world supply.

The Agency contacted all Marketing Authorisation Holders (MAHs) of centrally authorised radiolabelled medicinal products to assess the situation. There are currently 8 approved centrally authorised products. Seven out of 8 of those centralised products are labelled with radionuclides produced in reactors and they would be affected by recurring problems of the reactors. In addition in Europe there are more than 20 types of other radiopharmaceuticals (labelled or to be labelled with radionuclides produced in reactors) approved by national procedures which would also be affected.

The reactors currently used in the Europe and worldwide for the production of radionuclides are old and most of them will have to permanently close down by 2015. Other reactors currently used for research purposes could be "upgraded" in the future to be used also for production of radionuclides. Thus, there seemed to be a need to make an inventory of the reactors and their production capabilities as well as the current and future need of radiopharmaceuticals labelled with radionuclides produced in reactors in the EU.

This issue was discussed by the Committee for Medicinal Products for Human Use (CHMP) which was of the view that the place of those radiopharmaceuticals in clinical practice needed to be better understood in the longer term. In addition consideration should be given to alternative diagnostic/therapeutic procedures (including those currently available as well as new emerging options).

The Agency proposed to make best use of the available scientific expertise in the Europe by consulting the CHMP Scientific Advisory Group on Diagnostics, reinforced with additional experts, and to organise a scientific Workshop to broadly discuss the issue. It was recommended that all stakeholders, Nuclear Medicine physicians (e.g. European Association of Nuclear Medicine (EANM), industry (e.g. Association of Imaging Producers & Equipment Suppliers (AIPES)), other clinicians and imaging specialists should be involved in this discussion.

The outcome of the Workshop including the proposed recommendations is reflected in this report.

1.2. The workshop and its objectives

A workshop was established involving all possible stakeholders ranging from Nuclear Medicine physicians to referring physicians, the EANM, European industry, academia, the CHMP, Member States represented by patients organisations and the European Commission.

The objective of this Workshop was to address the place of radiopharmaceuticals, *labelled with radionuclides produced in reactors*, in clinical practice in the EU and to shed light on the possible alternatives that are currently available and those that are very likely to become available in the future.

The Workshop participants covered the diagnostic and therapeutic uses of those radiopharmaceuticals, labelled with radionuclides produced in reactors, whose availability/supply may be at risk due to a reactor crisis. The workshop was organised by sessions, mainly with a Nuclear Medicine physician alternating with a referring clinician as speakers. The speakers were invited to focus on discussing the current use and future needs of the radiopharmaceuticals labelled with radionuclides produced in reactors in the area of his/her expertise, and on consideration of alternatives (currently available and those that are very likely to become available in the future) with other radiopharmaceuticals for Nuclear Medicine physicians and, for referring physicians, with methods not using radiopharmaceuticals. Speakers were requested to clearly present their conclusions. At the end of each session, the Chairs directed the discussion in which the audience was invited to comment and to participate. For each session, conclusions were prepared taking into account the views of the

corresponding speakers and the outcome of the discussions, and presented to the audience for final discussion.

In the diagnostic field, the focus was on technetium (^{99m}Tc) labelled radiopharmaceuticals, as technetium (^{99m}Tc) is used for most Nuclear Medicine diagnostic applications and obtained from molybdenum (^{99}Mo) currently produced in nuclear reactors. In detail, the first sessions considered the scintigraphic procedures requiring higher activities of technetium (^{99m}Tc), which presently are brain, cardiac and bone imaging. The group then looked at priority indications, aimed to consider those scintigraphies performed with lower activities of technetium (^{99m}Tc) but that, in case of deep shortage, could undermine the correct management of the patients. The diagnostic sessions closed with an overview of the results of the 2008 French consensus with recommendations for alternatives to manage the supply shortage of reactor-produced radionuclides in clinical practice.

In the therapeutic field, the focus was on the current use of various radiopharmaceuticals labelled with iodine (^{131}I), samarium (^{153}Sm), strontium (^{89}Sr), rhenium (^{186}Re), erbium (^{169}Er), yttrium (^{90}Y) and phosphorus (^{32}P). Three sessions were scheduled to discuss the therapeutic use in endocrinological diseases, in bone and joint pain relief, and in haematologic diseases and cancer.

2. Diagnostic use of radiopharmaceuticals labelled with radionuclides produced in reactors

2.1. Brain imaging

Technetium (^{99m}Tc) radiopharmaceuticals have been very important in brain imaging and the most important compounds have been those that image the cerebral blood flow distribution. Considering increases in longevity, the clinical indications of relevance for brain SPECT in Nuclear Medicine are thus neurodegenerative diseases, such as dementias and Parkinsonian syndromes. Above the age of 80 years it is expected that approximately 10-15% of the patient population will suffer from dementia. Movement disorders also play a major role, with more marginal numbers of scans being requested for epilepsy. Brain SPECT is currently of marginal use in cerebrovascular diseases and traumatic brain injury and of even minor importance is the use in primary brain cancer or metastasis.

Nuclear Medicine images are focussed on metabolism, blood flow and tissue function, rather than the anatomy for which CT and MR may be more appropriate, and it is important to have both the anatomical and the Nuclear Medicine possibilities available. This builds on the evolution of diagnosis and follow-up of brain disorders to include integrating different imaging techniques and imaging with different biomarkers (which may still be in development). In movement disorders for example, there is no scope for technetium (^{99m}Tc) cerebral blood flow radiopharmaceuticals alone, in particular when it comes to the differential diagnosis of atypical pathologies. On the other hand, although multimodality approaches are increasing, no substitution of technetium (^{99m}Tc) radiopharmaceuticals can be presently envisaged in some indications, such as for pre-surgical evaluation in adults and children with pharmaco-resistant epilepsy where brain SPECT plays a crucial role in ictal localisation of epileptogenic foci.

Currently, there are some radiopharmaceuticals as alternatives to technetium (^{99m}Tc) tracers in brain imaging which may not be affected by the potential shortage of technetium (^{99m}Tc). Those alternatives include radiopharmaceuticals labelled with iodine (^{123}I), such as ioflupane (^{123}I) that is useful for imaging of most patients with movement disorders. For brain tumour imaging, the off-label use of technetium (^{99m}Tc) sestamibi may be substituted by thallous (^{201}Tl) chloride and radiolabelled aminoacids. Positron emission tomography (PET) radiopharmaceuticals can also be used as alternatives in some cases (although they may not be approved in all Member States): fludeoxyglucose (^{18}F) in dementia and for inter-ictal localisation of epileptogenic foci, radiolabelled aminoacids for brain tumours and fluorodopa (^{18}F) for imaging in movement disorders. Those PET radiopharmaceuticals labelled with radionuclides of very short physical half-life (e.g. those labelled with carbon (^{11}C) or oxygen (^{15}O)), although in certain circumstances advantageous, require the existence of a cyclotron on site, which is not widely available. In the diagnosis of dementia, PET with fludeoxyglucose (^{18}F) has shown better accuracy than SPECT with technetium (^{99m}Tc) cerebral blood flow compounds (but with similar patterns) and therefore could be the preferred tool.

In theory all technetium (^{99m}Tc) brain SPECT scans could be replaced by brain PET scans, but the current limited availability and higher price of the latter must be considered. Whilst some experts argue on an increase of 18% per year in the number of brain SPECT scans in Europe (with ^{99m}Tc or

^{123}I), it is noted that technetium (^{99m}Tc) radiopharmaceuticals are currently the cheapest and widely available compounds used in most scanners. Brain SPECT is thus less expensive than brain PET when it comes to the single investigation with accuracy enough for most patients, but the PET scanner has a higher throughput which could potentially render it more efficient. However, distribution of the number of brain imaging procedures across different European countries is variable, and it is likely that those countries that use a very low number of imaging studies will have fewer scanners, particularly PET scanners.

For evaluation of stroke and traumatic brain injury, brain SPECT with technetium (^{99m}Tc) blood flow radiopharmaceuticals are outpaced by MRI and MRI derived techniques.

2.2. Cardiac imaging and examination

Myocardial perfusion/viability scintigraphy (MPS) and radionuclide ventriculography play an important role in cardiac imaging and examination, with technetium (^{99m}Tc) radiopharmaceuticals being the tracers most widely used. According to the European Council on Nuclear Cardiology survey performed in 2005[1], the estimated number of MPS with technetium (^{99m}Tc) compounds done per million of inhabitants is around 2000; and according to other surveys, this number is expected to growth to 5-10% increase/year.

Currently, the main indications for use of cardiac imaging with radiopharmaceuticals include detection of coronary artery disease in symptomatic patients and in patients without ischaemic equivalent, risk assessment in various settings (patients with prior test result and/or known chronic stable cardiac artery disease, in patients after revascularisation, in the preoperative evaluation for non-cardiac surgery without active cardiac conditions and within three months of an acute coronary syndrome), assessment of viability and evaluation of ventricular function. The cardiac imaging modality most commonly used in Europe is still MPS with technetium (^{99m}Tc) radiopharmaceuticals, although other tests are also available and complementary such as perfusion PET, stress echocardiography, perfusion by magnetic resonance (cMRI) and coronary computed tomography (cCTA). Cardiac imaging using various modalities will continue to develop. Evidence-based comparative studies for different imaging techniques are more critical than ever.

Some radiopharmaceuticals as alternatives to technetium (^{99m}Tc) tracers in cardiac imaging include thallous (^{201}Tl) chloride, rubidium (^{82}Rb) chloride, ammonia (^{13}N), water (^{15}O) or fludeoxyglucose (^{18}F). Although some PET compounds are alternatives which could be more favourable than technetium (^{99m}Tc) radiopharmaceuticals in terms of kinetics (e.g., rubidium (^{82}Rb), ammonia (^{13}N)), they are still not licensed and the additional costs related to logistics, availability of PET machines and the weight of non-possibility to perform exercise stress tests or the need for on-site cyclotrons (e.g. in case of labelled ammonia or water) are not negligible. There are nevertheless advantages in alternative techniques, some of which could potentially allow for lower radiation exposures and better time management of patients. It is to be noted however that, as alternatives are encouraged, the multimodality approach is still envisaged in the future and technetium (^{99m}Tc) will still play a very important role.

Software and/or hardware solutions are available and could be used to optimise the injected activity of technetium (^{99m}Tc). Software solutions, although originally designed for short-time acquisitions, could be feasible for low dose studies, e.g. using half the activity of technetium (^{99m}Tc) and could potentially decrease the use of technetium (^{99m}Tc). Hardware solutions originally designed for very short-time acquisition studies include new detectors with higher sensitivity and improved resolution. These are however costly dedicated systems.

Bearing in mind that the number of tests of cardiac imaging with technetium (^{99m}Tc) radiopharmaceuticals will increase, there is a need to explore plausible alternatives to deal with technetium (^{99m}Tc) shortage which will also include the selection of the appropriate patients to be tested. Potential savings in technetium (^{99m}Tc) are thus multifactorial. Selection of imaging procedures for each indication and the strategy to deal with technetium (^{99m}Tc) shortage will depend on the availability or quality of equipment and trained staff.

[1] Underwood SR, Wiener S. Myocardial perfusion scintigraphy in Europe 2005: a survey of the European Council on Nuclear Cardiology. Eur J Nucl Med Mol Imaging 2009; 36(2): 260-268.

2.3. Bone imaging

After cardiac imaging and examination, bone imaging is estimated to be the area of highest consumption of technetium (^{99m}Tc), with technetium (^{99m}Tc) radiopharmaceuticals still being used in indications such as bone infection and inflammation or bone marrow imaging, and in Traumatology, Rheumatology and Oncology indications. In 2008 about 2 million of bone scintigraphies were performed in 15 European countries.

The multimodality approach is also of relevance in bone imaging, with several diagnostic modalities available in addition to Nuclear Medicine techniques (such as X-ray, ultrasound, MRI and CT). Alternatives to bone imaging with technetium (^{99m}Tc) radiopharmaceuticals are available (e.g. bone CT, PET with fludeoxyglucose (^{18}F), fluorocholine (^{18}F) or sodium fluoride (^{18}F), scintigraphy with indium (^{111}In) oxinate leukocytes, thallous (^{201}Tl) chloride, gallium (^{67}Ga) citrate or MRI) and they are the recommended modality of choice in some indications. Although, the use of technetium (^{99m}Tc) in bone imaging may be decreasing, it still plays a role in the diagnosis and localisation of several conditions (e.g. bone infection and inflammation and in Oncology) as metabolic disease always precedes morphological changes. In case of shortage of technetium (^{99m}Tc), examinations could be deferred in conditions such as trauma. Contrarily, there is presently no way to avoid bone imaging with technetium (^{99m}Tc) compounds in stress fractures and for better indication of surgery in osteoid osteoma.

It is understood that the metabolic and functional imaging qualities of Nuclear Medicine are of importance. However, PET with fludeoxyglucose (^{18}F), fluorocholine (^{18}F) or sodium fluoride (^{18}F), which allows for anatomical imaging as well, is a growing alternative of interest in several indications in oncology, bone infection, and probably in the future in traumatology. Attention should be paid to the need to register the PET radiopharmaceutical, and the availability of PET cameras, radiopharmaceuticals and cyclotrons, as previously mentioned.

SPECT-CT use is also increasing in bone infection. In some countries, indium (^{111}In) oxinate leukocytes and gallium (^{67}Ga) citrate are considered as alternatives, e.g. in bone infection, if technetium (^{99m}Tc) labelled leukocytes are not available.

In the future, there are different expectations regarding the use of modalities such as MRI, including whole body MRI and PET-MR, as hardware improves and alternatives become available. The use of technetium (^{99m}Tc) will potentially decrease, and the potential substitution of SPECT is probable. It is difficult to understand the timings associated with the evolution of alternatives.

2.4. "Priority" indications

Paediatric scintigraphy

Technetium (^{99m}Tc) radiopharmaceuticals are used in several indications in children, in particular when the alternatives are more irradiating or do not bring functional information which is relevant for the management of the patient. This is the case of dynamic renography, renal scintigraphy and radionuclide cystography with technetium (^{99m}Tc) compounds, and of rarer indications such as Merckel's diverticulum scintigraphy. Of relevance, are renal malformations and urinary tract infections, which are frequent in children. Imaging of the renal tract in paediatrics relies highly on ultrasound and Nuclear Medicine techniques, the later providing information on renal function.
The most commonly used radiopharmaceuticals in kidney imaging are technetium (^{99m}Tc) labelled. Imaging alternatives such as intravenous urography and CT are less effective and associated with higher radiation exposure and contrast-related side effects, and MRI for example requires sedation. In the case of a major shortage of technetium (^{99m}Tc), sodium iodohippurate (^{123}I) could be used as an alternative for dynamic renography.
Nuclear Medicine remains a priority in paediatric scintigraphy, in particular in Nephrology, due the small amount of technetium (^{99m}Tc) injected and potential for safe repetition of the test, the lack of contrast-related side effects, and its important functional advantages (e.g. differentiation between an obstructive and non obstructive uretherohydronephrosis supports the decision between surgical or non-surgical treatment).

Sentinel lymph node scintigraphy and intraoperative detection (SLNS)

The sentinel lymph node is the node on a direct drain pathway from the primary cancer. Location of an affected sentinel lymph node allows a decision, on the need for an extensive nodal dissection. Indications for sentinel node biopsy include different types of cancer, breast and melanoma being those with the highest frequency for referral, although the indications may vary. It is expected that the frequency of the indications will increase during the next years, and the effect of lack of technetium (^{99m}Tc) is noted as crucial. A shortage of technetium (^{99m}Tc) labelled radiopharmaceuticals would render the identification of the correct lymph basin impossible. Alternatives e.g. in breast cancer patients using blue dye, may not be advantageous as the sentinel node may, for example, not be located in the axillary region. A multimodal approach is needed where technetium (^{99m}Tc) still plays an essential role, in particular as this is well designed for the use of a surgical probe which then allows the location of affected nodes.

Imaging of hyper-functioning parathyroid glands by scintigraphy and intraoperative detection

The number of patients with hyperparathyroidism is increasing with aging, in particular in women. Hyperparathyroidism treatment of choice is surgery, with resection of the hyperfunctioning gland in primary hyperparathyroidism or complete or partial removal of the glands in secondary and tertiary hyperthyroidism. The efficacy of surgery is judged on the normalisation of calcaemia and decrease in PTH serum levels. It is consensus that imaging of the parathyroid glands is obtained before, during and after the surgical intervention. Parathyroid scintigraphy reveals hyperfunctioning glands, using available radiopharmaceuticals such as technetium (^{99m}Tc) compounds or thallous (^{201}Tl) chloride, although the later is less sensitive and more irradiating and thus cannot substitute technetium (^{99m}Tc) compounds. Sodium iodide (^{123}I) could potentially be used for thyroid gland imaging performed for subtraction. Ultrasound, although a non radiation emitting technique, is a subjective technique highly depended on the operator for its interpretation, and appears in fact complementary to technetium (^{99m}Tc) sestamibi scintigraphy for the best surgical approach. Whilst CT and MRI are only to be recommended when previous tests were negative, PET-CT with L-Methionine ([^{11}C]methyl) could be an interesting substitute although does not constitute a real alternative at present since it is neither licensed nor widely available requiring a cyclotron on site, and cannot be used for intraoperative detection. Therefore, the detection of hyperfunctioning parathyroid glands remains a priority in case of limited availability of technetium (^{99m}Tc).

Lung scintigraphy

Pulmonary embolism is a common and potentially fatal disease. An incidence of 700,000 new cases/year is expected, increasing with increasing age making it a major problem among the elderly. Perfusion scintigraphy is of relevance in diagnosing pulmonary embolism as well as at establishing the degree of perfusion restoration after an acute episode, and for chronic thromboembolic pulmonary hypertension. It has also been used, among others, for preoperative evaluation in lung cancer and also in patients with severe emphysema who are candidate for lung volume reduction surgery. However, over the years CT angiography has become the technique of choice for diagnosing pulmonary embolism. CT angiography is nevertheless not always feasible, as it is contraindicated in patients with renal failure or abnormal creatinine serum levels, critical illness, ventilatory support, hypersensitivity to iodine contrast media, possible pregnancy, among others. In these populations where CT is contraindicated, lung scintigraphy could be the modality of choice. The best specificity is obtained by associating scintigraphy of the perfusion and also of the ventilation of the lungs. The activity of technetium (^{99m}Tc) needed for perfusion lung scintigraphy is very low; in case of shortage of supply of technetium (^{99m}Tc) radiopharmaceuticals, krypton (^{91m}Kr) could be an alternative for ventilation studies where available.
Lung scintigraphy thus remains an indication of priority, in particular in children and in pregnancy, as it requires minimal invasion, it has no contraindications, and it accommodates less radiation burden than CT.

2.5. Other diagnostic uses of radiopharmaceuticals

The 2008 French consensus on management of technetium (^{99m}Tc) shortage was presented and discussed. Results of the French experience aimed to give recommendations for alternatives to scintigraphy with radiopharmaceuticals labelled with radionuclides produced in reactors by using other Nuclear Medicine alternatives or other imaging modalities in case of shortage of those radiopharmaceuticals, thus proposing principles for an optimal use of the available technetium (^{99m}Tc) resource, i.e., delaying non-urgent examinations, recommending alternatives, establishing the most frequent indications treated and identifying the priority indications.

3. Therapeutic use of radiopharmaceuticals labelled with radionuclides produced in reactors

3.1. Use of iodine (^{131}I) compounds for hyperthyroidism and thyroid cancer, and for other endocrinological malignancies

Radionuclide therapy in thyroid diseases and for other endocrine malignancies has since long included radioactive iodine (^{131}I). This therapy is widely used and requires trained specialised physicians.

Thyroid diseases requiring radionuclide therapy are hyperthyroidism (caused by toxic diffuse, toxic nodular and non-toxic goitre) and differentiated thyroid carcinoma. The use of sodium iodide (^{131}I) varies depending on the pathology and characteristics of the patient being treated, and it is recommended as a first line treatment in some indications but not in others. The activity used is also not harmonised and varies across practice.

Supply shortage is not expected for radiopharmaceuticals labelled with iodine (^{131}I). If it occurs, alternatives to sodium iodide (^{131}I) are available both for treatment of benign thyroid disease and for post-thyroidectomy thyroid imaging (pre-ablation, post-ablation and follow-up). In hyperthyroidism, the alternatives in case of sodium iodide (^{131}I) shortage include anti-thyroid drugs, with the caveat of a delayed therapeutic outcome (12-18 months treatment), possible allergic reactions and toxicity in a minority of patients; and surgery, with potential anaesthetic risk, parathyroid damage, recurrent/superior laryngeal nerve damage and recurrence if a total thyroidectomy is not performed. Scintigraphy with sodium iodide (^{123}I) and PET with iodine (^{124}I) are used in post-thyroidectomy imaging for detection of thyroid remnants and/or metastases, and also PET with fludeoxyglucose (^{18}F) to detect metastases which are not iodine-avid. These alternatives are of relevance in the management and follow up of patients.

For treatment of differentiated thyroid cancer, sodium iodide (^{131}I) is recommended for post-thyroidectomy radioiodine ablation in high risk patients and for therapy of iodine-avid recurrent or persistent differentiated thyroid cancer. In those cases, alternative treatments are however still experimental and not registered and thus sodium iodide (^{131}I) continues to play a very important role. Alternatives include novel therapies under evaluation, e.g. retinoids, radiolabelled somatostatin analogues, chemotherapy, kinase inhibitors and different radionuclide therapies (attention needed to be paid to the approval status in this indication) which sensitivity varies by tumour, including indium (^{111}In), yttrium (^{90}Y), lutetium (^{177}Lu), and rhenium ($^{186/188}$Re).

Despite the increased incidence of differentiated thyroid carcinoma, related to both the discovery of small tumours by modern techniques and the stabilisation with time in the number of patients with advanced disease, overall the use of sodium iodide (^{131}I) in this entity is diminishing. There are patterns of change in the referral of patients with reduced therapeutic use in patients with low risk disease foreseen, i.e., a greater percentage of small tumours will not be treated with sodium iodide (^{131}I). Moreover, the systematic diagnostic use of this radiopharmaceutical in the follow-up of differentiated cancer is declining as approved alternatives are available. On the other hand, the use of sodium iodide (^{131}I) is not expected to increase in hyperthyroidism.

The use of iobenguane (^{131}I) for treatment of endocrinel malignancies (mostly neuroblastoma and some medullary thyroid cancers) is low and an increase is not envisaged; alternatives are experimental.

3.2. Bone and joint pain relieving radiopharmaceuticals

In oncology, it is noted that the bone is a preferred site of metastasis for many solid cancers. Bone pain can be the first sign that the disease has spread. Pain restricts mobility and impairs sleep resulting in a decreased quality of life. Bone metastases can be osteoblastic and osteoclastic. The main use of radionuclide therapy is in the osteoblastic skeletal metastases, where bone remodelling is done, but some action has also been observed in osteoclastic metastases. Available radionuclides for treatment are used in single or multiple administrations and include three categories: beta (β) emitters (^{32}P, ^{89}Sr, ^{153}Sm, ^{186}Re, ^{177}Lu, ^{188}Re), alpha (α) emitters (^{223}Ra) or electron conversion emitters (^{117m}Sn). Only samarium (^{153}Sm) lexidronam, strontium (^{89}Sr) chloride and rhenium (^{186}Re) sulphide colloid are currently licensed radiopharmaceuticals for bone pain relief.

Although some experts argue good results with low toxicity, there is presently low use of radiopharmaceuticals for relief of bone pain in metastatic bone palliation procedures, and its use is promoted only as quality of life decreases and after other treatments. This is due, among others, to the fact that palliative agents had a limited acceptance within the Oncology community; there are a limited number of therapy units in Europe, and bone palliation has been promoted only in very late stages of the disease. There are available alternatives in case of shortages and these include palliative intended local radiotherapy, chemotherapy and therapy with bisphosphonates. It is also noted that, since there are several radiopharmaceuticals available for relief of bone pain, these could substitute for each other. Therefore, no significant short-term changes are expected in Europe, as the use of these agents is marginal in Oncology. However, as therapy progresses, the use of these radiopharmaceuticals may be indicated for an earlier stage of the disease as part of a new radiochemotherapy concept. It involves radio and chemotherapy co-administration, and may lead to an increase in the number of patients being treated with bone pain relieving radiopharmaceuticals but it is still under investigation.

Use of radiopharmaceuticals in palliation of painful joint is low in comparison to the potential number of candidates and no significant increase is expected. Radiosynovectomy involves the intra-articular injection of a radiopharmaceutical composed of yttrium (^{90}Y) citrate colloid, rhenium (^{186}Re) sulphide colloid or erbium (^{169}Er) citrate colloid. The choice of the radiopharmaceutical depends on the joint being treated, which is linked with the individual depth of penetration of the radionuclide in the affect joint. For local treatment, alternatives are available and include intra-articular glucocorticoids combined with immobilisation, surgical synovectomy and chemical synovectomy. The cost, availability and results, for example in induction of remission, are limitations of these alternatives. Less local treatments are given and the tendency is that systemic therapy starts earlier making current treatments more aggressive. When systemic treatment is considered (i.e. if more than 2 joints are affected), conventional anti-rheumatic drugs and biological agents are available, and limitations include the cost (linked with long term treatment), approval status, and safety profile of the different medicinal products.

No shortage of approved radiopharmaceuticals for bone and joint pain palliation is expected.

In case of shortage, there are different alternatives although consideration must be given to a different profile. The future needs are thus dependent on the development of protocols used to treat patients suffering from bone and joint pain.

3.3. Treatment of haematologic diseases and cancer (e.g. antibodies labelled with yttrium (^{90}Y) or iodine (^{131}I))

Radionuclide therapy for haematologic diseases and cancer is used in several indications, some of which are under investigation, including malignant lymphomas, high-risk acute myeloid leukaemia, polycythaemia vera, neuroendocrine tumours and liver cancer. Its scope is growing. The expected benefit of such therapy is to increase the cytotoxic effect on extended or multifocal neoplasias with high selectivity.

Radiopharmaceuticals approved in Europe for treatment of haematologic diseases and cancer include ibritumomab tiuxetan (^{90}Y) and sodium (^{32}P) phosphate. Increased use of radionuclide therapy in haematologic diseases and cancer, particularly using radiopharmaceuticals labelled with yttrium (^{90}Y) and lutetium (^{177}Lu), is expected.

In lymphoma, alternatives to ibritumomab tiuxetan (^{90}Y) within Europe are experimental: autologous stem cell transplantation, salvage regimens and the development of novel agents that may have a role in the future but which are not yet approved such as lutetium (^{177}Lu). No supply shortage of ibritumomab tiuxetan (^{90}Y) is expected.

In high-risk acute myeloid leukaemia, allogeneic stem cell transplantation is part of the standard treatment and the evidence of new therapeutics progresses. Treatment of this entity with radio-labelled monoclonal antibodies is still experimental.

In some indications the use of therapeutic radiopharmaceuticals is decreasing, e.g. in polycythaemia vera and essential thrombocytaemia, although there is a rare recommended indication for sodium phosphate (^{32}P) in patients >70 years where standard therapies are not feasible options. It is however noted that current long-term supply shortage of phosphorus (^{32}P) exists in some European countries, and thus this needs to be considered by the referring physician.

In neuroendocrine tumours there is presently no authorised radionuclide therapy, and peptide receptor radionuclide therapy is used off-label.

Selective internal radiation therapy with yttrium (^{90}Y) microspheres is approved as a medical device for treatment of liver cancer, but actually used as a radiopharmaceutical.

As protocols evolve, radionuclide therapy may be used at earlier stages, novel monoclonal antibody therapies may be developed and thus one can foresee an increase in the use of yttrium (^{90}Y) and lutetium (^{177}Lu) (once authorised). As lutetium (^{177}Lu) is not produced in reactors, in case of shortage of yttrium (^{90}Y), a shift can be anticipated, although there are limitations inherent to the characteristics of the radiopharmaceutical and the diseases being treated.

4. CONCLUSION AND RECOMMENDATION

Technetium (99mTc) is the most commonly used radionuclide in Nuclear Medicine, thus a shortage in its supply could have major consequences in several areas where Nuclear Medicine imaging provides support in diagnosis and follow-up of treatment.

The demand for technetium (99mTc) is increasing, in particular in Neurology and Cardiology, but its use for bone imaging could be decreasing as other alternatives become available. Some other Nuclear Medicine imaging techniques including PET, which do not involve technetium (99mTc) could be used in the future. It is noted that PET is currently highly dedicated mostly to Oncology and partly to Neurology but difficult to dedicate to Cardiology due to patient load and the lack of currently approved radiopharmaceuticals for myocardial perfusion. Considering the current restraints in availability of PET cameras, the currently limited approval of PET radiopharmaceuticals and the cost implications of the SPECT to PET switch, other alternatives may need to be considered at short term in case of confirmed technetium (99mTc) shortage. Options include but are not limited to thallous (201Tl) chloride for Cardiology or gallium (67Ga) citrate for infections (with increased irradiation), and reducing the activity of technetium (99mTc) per capita in particular by favouring the use of newer software or hardware with sensitive detectors.

Scintigraphy remains the modality of choice in some indications, and if available, non-technetium radionuclides could be favoured, e.g. sodium iodide (123I) for thyroid pathologies, or krypton (81mKr) for pulmonary ventilation, the shortage of technetium (99mTc) justifying the higher costs foreseen.

For some indications there are currently no identified alternatives to the use of technetium (99mTc) scintigraphy without encompassing a risk on patient management. Paediatric, sentinel node, parathyroid and lung scintigraphy with technetium (99mTc) labelled radiopharmaceuticals are essential and should be considered of priority in case of shortage of supply of technetium (99mTc). Consideration should be also given to the prioritisation of other indications such as intractable epilepsy or osteoid osteoma.

A supply shortage of licensed therapeutic radiopharmaceuticals is not expected at present, except for sodium phosphate (32P). Iodine (131I) will continue to play a major role in the treatment of thyroid diseases, although its systematic diagnostic use in follow-up of differentiated thyroid cancer is declining. The use of approved radiopharmaceuticals for therapy in haematological diseases and cancer will increase. However, several available radiopharmaceuticals for palliation of bone and joint pain might remain underused due to limited acceptance by prescribers.

Although there are alternatives to therapeutic radiopharmaceuticals within Nuclear Medicine, no approved alternative exist at all for certain specific settings such as for sodium iodide (131I) in the majority of patients with differentiated thyroid cancer, ibritumomab tiuxetan (90Y) in lymphomas, and for sodium phosphate (32P) in singular cases with polycythaemia vera or essential thrombocythaemia. Therapies with radiopharmaceuticals are evolving and in the future other alternatives may be expected, including in the field of solid tumours.

Based on the above there is the need to develop protocols to aid those physicians involved in the diagnosis and/or treatment of certain conditions to seek the best alternative, in case of shortage of supply of radiopharmaceuticals labelled with radionuclides produced in reactors. Attention should be given to correct patient management, and patient prioritisation cannot be excluded in certain situations. As practice may change due to potential shortage of supply of such radionuclides, it is very important to note that the above recommendations are based on retrospective collection of data by Nuclear Medicine physicians or referring physicians expert in their fields, and that recommendations to collect data prospectively need to be considered aiming to understand the consequences of this change to the clinical outcome.