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GUIDELINES

EANM procedure guideline for ^{32}P phosphate treatment of myeloproliferative diseases

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Abstract
Introduction ^{32}P phosphate was the first therapeutic radioisotope, used in leukaemia about 70 years ago. Since then, many new agents for haematological proliferations have been introduced successfully. Today there remains a distinct subgroup of elderly patients with polycythaemia vera and essential thrombocythaemia for whom ^{32}P is the most optimal treatment option, an assertion supported by two large studies with long follow-up.
Purpose The purpose of this guideline is to assist the nuclear medicine physician in treating and managing patients who may be candidates for ^{32}P phosphate therapy.

Keywords Guidelines · Nuclear medicine · ^{32}P phosphate · Polycythaemia vera · Essential thrombocythaemia · Radionuclide therapy

Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in:

1. Evaluating patients who might be candidates for ^{32}P phosphate treatment of myeloproliferative disease
2. Performing this treatment
3. Understanding and evaluating the sequelae of therapy

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Background information and definitions

Definitions

1. ^{32}P is a reactor-produced, pure beta-emitting radionuclide with a physical half-life of 14.3 days. The maximum and mean beta particle energies are 1.71 MeV and 0.695 MeV respectively. The mean particle range in tissue is 3 mm and the maximum range, 8 mm.
2. Therapy in this context means intravenous or oral administration of ^{32}P orthophosphate in aqueous solution.
3. Myeloproliferative disease in this context means polycythaemia vera and essential thrombocythaemia.

Background

^{32}P therapy has been an accepted treatment for myeloproliferative disease for more than 30 years.

Following intravenous administration, the radiopharmaceutical clears from the whole blood and plasma in a bi-exponential manner with fast components of 1.7 and 0.8 days, respectively, and a slow component of approximately 20 days. The biological half-life in bone marrow is 7–9 days. The highest radiation exposure occurs in the bone marrow, liver and spleen. ^{32}P is actively incorporated into the nucleic acids of rapidly proliferating cells. The radiopharmaceutical is used to suppress hyperproliferative cell lines rather than to eradicate them.

Indications

Polycythaemia vera (PV)

PV is a chronic progressive myeloproliferative disorder characterised by an absolute increase in red blood cell mass.

Leucocytosis, thrombocytosis and splenomegaly usually occur. Before therapy is initiated, the diagnosis of PV must be confirmed to exclude secondary causes of polycythaemia. PV is not a rare disease. Statistical data indicate an incidence of 1–2 per 100,000 per year, which increases with age. Management of patients below the age of 50 may be very different from that of patients older than 60. A major concern in managing younger patients is the development of spent-phase PV or acute leukaemia; a major issue in the elderly is thrombosis. Thus in the elderly, the clinical risk associated with this disease is essentially vascular, and the associated risk of mortality and sequelae is serious for the patient (quality of life) and for the community (high costs).

^{32}P is perfectly well tolerated and efficient in elderly patients (>65 years), and induces a long survival with an excellent quality of life. The potential severity of the disease may be assessed according to whether there is short-term relapse after the first ^{32}P-induced remission. After excluding patients with life-threatening vascular symptoms, 5-year survival was found not to be different in an age- and sex-matched population. ^{32}P treatment was associated neither with shorter survival nor with a higher incidence of acute myeloid leukaemia (AML) than treatment with busulfan or hydroxyurea. The incidence of AML 10 years after ^{32}P treatment was approximately 10% in two large series.^{32}P therapy is generally reserved for patients aged >65–70 years [1, 2].

Essential thrombocythaemia (ET)

ET is a chronic myeloproliferative disorder characterised by unremitting thrombocyte elevation. It is essential to exclude secondary causes of thrombocytosis. The disease is rare but it appears that the prevalence is increasing. The clinical risk for vascular diseases is the same as for PV. Treatment using ^{32}P is usually reserved for patients over the age of 65–70 years.

Contraindications

Absolute Pregnancy; breastfeeding

Relative The radiopharmaceutical is not recommended for women of childbearing age

PV Total white cell count $<2.0\times10^9$/l; rapidly deteriorating renal function

ET Total white cell count $<2.0\times10^9$/l; haemoglobin<90 g/l; rapidly deteriorating renal function

Procedure

Facility and personnel

The facilities required will depend on national legislation concerning the emission of pure beta-emitting therapy agents. If in-patient treatment is required by national legislation, this should take place in an approved facility with appropriately shielded rooms and en-suite bathroom facilities.

The facility in which treatment is administered must have appropriate personnel, radiation safety equipment, and procedures available for waste handling and disposal, handling of contamination, monitoring of personnel for accidental contamination and controlling contamination spread.

Appropriately trained medical staff with supporting nursing staff should undertake the administration of ^{32}P.

Physicians responsible for treating patients should have an understanding of the clinical pathophysiology and natural history of the disease processes, should be familiar with other forms of therapy and should be able to liaise closely with other physicians involved in managing the patient.

Clinicians involved in unsealed source therapy must be knowledgeable about and compliant with all applicable national and local legislation and regulations.

Patient preparation and data required

Patients with PV should be pre-treated with venesection to reduce the haematocrit to 42–47%.

Chemotherapy should be discontinued within 1 week after ^{32}P administration.

Recent blood count, kidney function and weight should be acquired.

Patient information and instruction

Patients should receive both written and verbal information about the procedure prior to receiving therapy. Informed written consent must be obtained from the patient.

Administration

The radiopharmaceutical is administered by intravenous injection or orally.

The activity generally used is either 74–111 MBq/m^2 body surface (2–3 mCi/m^2) with a maximum upper activity limit of 185 MBq (5 mCi), or a slightly higher activity of 3.7 MBq/kg body weight (0.1 mCi/kg) with a maximum upper activity limit of 260 MBq (7 mCi), which in practice

means a fixed activity above 70 kg body weight. A decrease in activity of 25% in patients >80 years of age is recommended by some investigators.

An alternative, dose-escalating approach is to administer a fixed lower dose of 111 MBq (3 mCi). In the absence of an "adequate response" (i.e. PV: haematocrit <47%; thrombocyte and leucocyte reduction >25%; ET: thrombocytes $<450\times10^9$/l), a second treatment is to be given after 3 months, this time with a 25% increase in dose. This procedure of dose augmentation may be repeated every 3 months until an adequate response is obtained. The maximum upper activity limit for a single administration is 260 MBq (7 mCi).

Adequate response duration may be months to several years. Re-treatment at progressive disease is feasible.

Precautions, follow-up and side-effects

The treating clinician must advise the patient on reducing unnecessary radiation exposure to family members and the public.

Following treatment, patients should avoid pregnancy for at least 4 months. In reality, it is unlikely that women of childbearing age will be eligible for ^{32}P therapy.

Excretion in urine is of particular concern during the first 2 days post administration. Patients should be advised to observe rigorous hygiene in order to avoid contaminating groups at risk using the same toilet facility.

If inpatient treatment is required, nursing personnel must be instructed in radiation safety. Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency. Concern about radiation exposure should not interfere with the prompt appropriate medical treatment of the patient.

Haematological monitoring is essential post therapy to exclude significant myelosuppression and plan subsequent treatment cycles, with checking of blood counts usually every 4–6 weeks.

The use of oestrogens or androgens can alter the biodistribution of ^{32}P.

Side-effects

Early Leucopenia and thrombocytopenia are generally observed at 4–6 weeks and resolve spontaneously by 4 months.

Late PV is associated with an increased risk of acute leukaemia. Chlorambucil, busulfan and ^{32}P are all examples of therapy that have been shown to be leukaemogenic. Several studies have suggested the potential leukaemogenicity of hydroxyurea but no randomised studies have yet been conducted. Regarding the two newest agents used for PV and ET, interferon-alpha and anagrelide, both have been studied for efficacy but their influence on the potential for leukaemic transformation has not been well studied to date.

The incidence of leukaemia is further increased in patients treated with ^{32}P and varies between 2% and 15% at 10 years. This incidence is comparable with that associated with the chemotherapeutic regimens commonly used in the management of this condition. However, no significant dose-effect relationship for leukaemic risk has been observed in two contemporary series with a long follow-up.

Radiopharmaceutical

Approved name Sodium [^{32}P] phosphate

Labelling The radionuclide is supplied in a ready-to-use form of orthophosphate [PO_4^{3-}] in aqueous solution.

Dosimetry The table lists the organs with the highest radiation absorbed dose and the effective dose equivalent (EDE) in adults.

Organ	mGy/MBq
Bone surface	1.1 E+01
Red bone marrow	1.1 E+01
Breasts	9.2 E-01
Adrenals	7.4 E-01
Bladder surface	7.4 E-01
Stomach wall	7.4 E-01
Small intestine	7.4 E-01
Upper large intestine wall	7.4 E-01
EDE	2.2 E+00

Source: ICRP publication number 53

Quality control The amount of activity to be administered should be checked using an isotope calibrator.

Issues requiring further clarification

The role of ^{32}P in the management of PV and ET is continuously under review.

^{32}P is perfectly well tolerated and efficient in elderly patients with PV and induces a long survival with an excellent quality of life [1, 2]. In younger patients with PV or ET other agents with probably less pronounced

long-term risks should be used, e.g. interferon-alpha and anagrelide [3, 4, 5].

Disclaimer

The European Association of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high-quality nuclear medicine procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

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ERRATUM

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Additional notes to the section headed "Dosimetry" are listed below.

Dosimetry. The table lists the organs with the highest radiation absorbed dose: bone surface, red bone marrow and breasts [1]. All other major organs and/or organ systems receive the same absorbed radiation dose per unit administered activity (Table 1).

The "effective dose equivalent" (EDE) is no longer in use; it has been replaced by the "effective dose" (ED) [3]. The ED reflects the stochastic risk of radiation and may be inappropriate for the assessment of the risk associated with non-stochastic radiation effects in targeted radionuclide therapy.

It should be noted that the absorbed doses given in the table were derived from a metabolic biokinetic model for occupational exposure of workers [4].

Table 1 Organ absorbed doses per unit administered activity after injection of ^{32}P

Organ	mGy/MBq
Bone surface	1.1 E+01
Red bone marrow	1.1 E+01
Breasts	9.2 E-01
Other major organs	7.4 E-01
Effective dose [2]	2.4 E 00 mSv/MBq

The absorbed doses per unit administered activity given in this guideline should neither be applied to practical dosimetry for an individual patient in a therapeutic setting nor be used prospectively for the prediction of the treatment-related toxicity in an individual patient.

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