

³²P phosphate Treatment of Myeloproliferative Diseases

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1. Introduction

³²P phosphate was the first therapeutic radio-isotope. It was first 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 ³²P is the most optimal treatment option, an assertion supported by two large studies with long term follow-up and it has been an accepted treatment for myeloproliferative disease for more than 30 years.

Following intravenous administration, the radiopharmaceutical is cleared 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. ³²P 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.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. 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. Statistical data indicate an incidence of 1-2 per 100.000 per year, which increases with age.
- 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 ³²P 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 $<2,0 \times 10^9/l$; rapidly deteriorating renal function

- ET Total white cell count <2,0 × 10⁹/l; haemoglobin <90 g/l; rapidly deteriorating renal function

4. Relation to other therapies

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. The associated risk of mortality and other sequelae is significant for the patient (quality of life) and for the community (high costs). ³²P is well tolerated and efficient in elderly patients (>65 years). It 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 ³²P-induced remission. After excluding patients with life-threatening vascular symptoms, the 5-year survival was found not to differ from an age- and sex-matched population. ³²P treatment was neither associated with shorter survival nor with a higher incidence of acute myeloid leukaemia (AML) compared to treatment with busulfan or hydroxyurea. The incidence of AML 10 years after ³²P treatment was approximately 10% in two large series. ³²P therapy is generally reserved for patients aged >65-70 years.

5. Medical information necessary for planning

Recent full blood count, kidney function and weight.

6. Radiopharmaceutical:

Sodium [³²P] phosphate

Activity: 74-111 MBq/m² body surface (2-3 mCi/m²) 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 25 % decrease in activity 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 <450×10⁹/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).

Administration: The radiopharmaceutical is administered either by intravenous injection or orally.

7. Radiation safety

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
<u>EDE</u>	<u>2,2 E+00</u>

Source: ICRP publication number 53

8. Patient preparation/essentials for procedure

Patients with PV should be pre-treated with venesection to reduce the haematocrit to 42-47%. Chemotherapy should be discontinued within 1 week after ³²P administration. ³²P administration. Recent blood count, kidney function and weight should be known.

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.

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 ³²P 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 on 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 and appropriate medical treatment of the patient.

Haematological monitoring is essential post therapy to exclude significant myelosuppression and plan subsequent treatment cycles (full blood count usually to be checked every 4-6 weeks).

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

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 ³²P 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 ³²P 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 long term follow-up.

9. Report

The report to the referring physician should include the fact that informed consent was obtained and that the patient is aware of possible leukopenia, thrombocytopenia, and late side effects (this should alert the referring physician to monitor the patient).

The referring physician may be reminded that haematological monitoring is essential post therapy to exclude significant myelosuppression and to plan subsequent treatment cycles. Usually the full blood count is checked every 4-6 weeks. Re-treatment of progressive disease is feasible.

Following treatment, patients (women of childbearing age) should avoid pregnancy for at least 4 months.

10. Literature

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