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POINTS TO CONSIDER CONCERNING ENDPOINTS IN CLINICAL STUDIES WITH HAEMATOPOIETIC GROWTH FACTORS FOR MOBILISATION OF AUTOLOGOUS STEM CELLS

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

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POINTS TO CONSIDER CONCERNING ENDPOINTS IN CLINICAL STUDIES WITH HAEMATOPOIETIC GROWTH FACTORS FOR MOBILISATION OF AUTOLOGOUS STEM CELLS

1. PREAMBLE

Haematopoietic stem cell preparation and transplantation is a rapidly developing area, allowing a large number of potential sources of stem cells, of methods to improve their collection and/or manipulation *in vitro* or *in vivo* to be utilised. Due to the diversity of applications and also of substances apart from cytokines, which may be the subject of applications in the future, it cannot be the intention of this "points to consider paper" to clarify and regulate all potential trial designs addressing such issues. Far more important is the intention to indicate, that the CPMP is becoming aware of the substantial development in this field and of the necessity to provide some basic information helpful in designing adequate trials. Advice by experts of the CPMP may be sought prior to the study design.

The initiative for this points to consider document comes from the CPMP discussions on autologous stem cell preparation, and therefore is primarily addressing this issue. However, some more general statements are made.

This points to consider document should be read in conjunction with the Note for Guidance on "Clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy" (CPMP/EWP/555/96).

2. INTRODUCTION

2.1 General aspects

Allogeneic transplantation of haematopoietic stem cells from an HLA-identical donor was introduced initially for patients with neoplasias of the haematopoietic system. They received extremely high-dose chemotherapy plus/minus total body irradiation followed by the donor stem cells, thus without the risk of contamination of the host with neoplastic cells.

Autologous stem cell transplantation also relies on the hypothesis that high-dose chemotherapy may provide a higher cure rate in neoplastic diseases. The collection of stem cells or haematopoietic precursor cells from bone marrow or peripheral blood and their re-infusion after cytotoxic treatment provides faster haematopoietic recovery and decreases the risk for severe infection/bleeding or even death of patients. In contrast to the allogeneic setting, potential re-population of the host with tumour cells possibly contaminating the stem cell product and their potential stimulation *via* the harvesting manoeuvre is an issue. Attempts are therefore directed to develop new methods designed to increase the purity of the stem cell product by positive and/or negative selection procedures. This may decrease the stem cell yield substantially and efforts are undertaken for an *in vitro* expansion and manipulation of small numbers of long-term culture initiating cells (LTCIC). Furthermore, scenarios can be envisaged where subsets of progenitor cells are collected and/or expanded. For a practical purpose this points to consider paper refers to the current standard type of progenitor cell transplantation, in which measurement of $CD34^+$ cells is a major tool for the performance and for directing the procedure.

It has to be considered that the procedure of the stem cell preparation by itself is only a part of the total treatment plan. Mostly, the benefit/side effect ratio will be determined by the toxicity of the antineoplastic regimen and the response of the tumour. Thus, even a significantly more toxic new preparation regimen would seem acceptable, provided that the intercurrent side effects were outweighed by a higher number of successful transplantations and a superior

final outcome of the tumour disease. On the other hand, a pure increase in $CD34^+$ cell counts might seem modest progress, if not translated into a higher number of patients undergoing successful transplantation. These aspects should be considered for the rationale and design of a particular study.

2.2 Sources of stem cells

The sources of stem cells/progenitor cells that are considered in this document are autologous peripheral blood stem cells (PBSC), mobilised from bone marrow into peripheral blood to be used for autologous stem cell transplantation. Allogeneic PBSC and umbilical cord vein stem cells are not considered in this document.

2.3 Mobilisation, collection and preparation of stem cells

The rationale for all aspects of stem cell transplantation must be strictly defined by the applicant, regarding the substance/combination used for mobilisation, the dosage and schedule of each substance within the regimen, the collection procedure and the procedure for surveying cell numbers. This has to be based on current standards and as recommended by relevant societies or respective literature.

- **Note:** Methods for standardisation of $CD34^+$ cells have been published e.g. by the International Society for Hematology and Graft Engineering [*Sutherland et al., The ISHAGE guidelines for $CD34^+$ cell determination by flow cytometry: International Society of Hematology and Graft Engineering. J Hematotherapy, 5,213,1996*].
  Instructions are also provided by the EBMT handbook [*Dreger P, Schmitz N: Sources of stem cells, Chapter 6, p72-86, in: The EBMT Handbook, Blood and Bone Marrow Transplantation. Apperley J, Gluckman E, Gratwohl A, Editors, ESH, 1998*].

As long as multicentre evaluations of stem cells or $CD34^+$ cells are performed, studies on the reproducibility of all parts of the stem cell preparation procedure, in particular of methods to determine the quality and number of $CD34^+$ cells, must accompany an evaluation of the clinical efficacy of a particular substance on stem cell yield.

3. SELECTION OF PATIENTS

As far as possible, patients should be homogenous concerning basic diseases, since they might differ substantially in marrow infiltration, contaminating neoplastic cells, myelosuppressive stem cell toxic pre-treatment and previous radiotherapy.

In cases where patients with different basic diseases are included the rationale should be provided. Individual studies on a specific disease should be sufficiently powered to allow direct conclusions. Retrospective meta-analysis of pooled data without *a priori* stratification is discouraged.

3.1 Treatment of patients with previously established failure for stem cell mobilisation

Patients having failed previous attempts to mobilise and collect a sufficient number of stem cells, allowing them to proceed to transplantation by standard means (in particular by a standard cytokine or a combination of a standard cytokine plus chemotherapy), are extremely valuable for determining the potential efficacy of a new cytokine/substance.

3.2 Treatment of patients who are at risk for poor mobilisation

Under certain circumstances – which have to be justified by the applicant – it may be possible to define patients with an *a priori* increased risk of poor mobilisation or mobilisation failure because of the underlying neoplastic disease (degree of marrow infiltration), age, number and type of prior treatment regimens (distribution of weighted risk factors).

3.3 Patients with a standard and low risk for poor mobilisation

In cases where the primary endpoint of a new cytokine/substance would be improved toxicity as compared to a standard regimen standard risk patients may be adequate. Sufficient evidence for a beneficial risk/benefit ratio must exist prior to study and must be justified by the applicant.

4. STUDIES ON THE ASSESSMENT OF SUBSTANCES FOR STEM CELL COLLECTION AND TRANSPLANTATION

4.1 Phase II studies

4.1.1 Objectives

The objective of phase II studies is to select the optimal dosing schedule and combination and to obtain preliminary evidence of efficacy and safety of the new drug either alone or in combination with other drugs. Ideally, the study should include a control arm with a standard regimen in order to get preliminary evidence of the relative efficacy and safety of the standard and new approaches. It may be necessary to test different sequences of the application of the new substance within a combination regimen (with other cytokines or chemotherapy) in order to define the regimen to be tested in phase III studies.

4.1.2 Study population

Homogeneous groups of patients, who are candidates for stem cell transplantation. Groups of patients mobilised with HGF ± chemotherapy (as justified by the applicant) should be investigated. Dependent on the toxicity profile the following groups of patients can be included:

a) patients who have failed standard mobilisation techniques

b) patients who according to established criteria are at risk for poor mobilisation

c) patients who are at standard risk (included only in the inferior toxicity situation)

4.1.3 Study design

Whenever possible, studies should be randomised for all populations mentioned above.

4.1.4 Primary endpoint

- Usually the percentage of patients achieving the minimal (=$2x10^6$/kg) number of $CD34^+$ cells considered necessary and safe to proceed to autotransplantation

or

- an adequate toxicity marker (which has to be selected according to the toxicity profile of the substances/regimens compared) in the inferior toxicity situation

will be considered the primary endpoint of the study.

Other options concerning the number of $CD34^+$ cells have to be justified by the applicant.

4.1.5 Secondary endpoints

- Biomarkers for clinical efficacy (optimal dose of $CD34^+$ cells [i.e. $5x10^6$/kg] or target dose of $CD34^+$ cells as defined by the applicant, number of aphereses or large volume aphereses necessary to obtain the minimal number of $CD34^+$ cells necessary for autotransplantation, number of $CD34^+$ cells/kg/apheresis)
- the number of patients proceeding to autotransplantation (any reasons why patients were not autografted, including progression of their malignant disease, etc., must be listed)

- the number of patients reaching engraftment of absolute neutrophil count (ANC) or platelets
- the number of patients becoming transfusion-independent
- time to ANC >0.5 x 10^9/l and thrombocytes >20 and >50 x 10^9/l with independence from transfusions
- severe side effects/complications (WHO grade III/IV bleedings and infections, days in intensive care units, etc.) during engraftment period

4.1.6 Safety parameters

In general, adverse reactions or side effects should be reported separately for both the phase in which stem cells are being collected and the time after reinfusion of stem cells. The following parameters should be included:

- standard toxicity parameters
- adverse reactions or side effects of the mobilisation procedure (thromboses, bleedings, central line complications), analysed according to the number and type of aphereses performed
- the number of days with fever and iv-antibiotics

4.2 Phase III studies

4.2.1 Objectives

The objective of a phase III study is to confirm the clinical efficacy and safety of the proposed regimen(s) for the new HGF/combination and to prove a clinical benefit for the patient population compared to mobilisation (and subsequent transplantation) with standard methods.

4.2.2 Study population

The study population selected usually should be identical to that described for phase II studies, if not otherwise justified by the applicant, and representative of the indication requested.

4.2.3 Study design

Randomised clinical trials are necessary. Since a standard regimen exists, it is recognised that a placebo-alone arm cannot be used. Potential comparators for a new cytokine/substance are a standard cytokine like G-CSF alone, a chemotherapy mobilisation program or the combination of both. The applicant should provide sufficient rationale and information on the type, schedule and dose of comparator used, which should comprise the regimen considered most efficient for the situation of the patient. With the ongoing discussion of the best dosage regimen for the standard therapy there may be a need for more than one control arm and there may be a need to examine the new drug in more than one regimen.

For patients as defined in section 3.3., in whom equivalence in efficacy but superiority in the tolerability of the new regimen/substance are the goal of the study, a less effective regimen may be used as a comparator, provided that a sufficient number of stem cells is achieved and patients proceed to and successfully complete autotransplantation.

In case cytokine combinations (new cytokine + standard cytokine) are compared with a standard cytokine alone and if there is evidence from the literature that a higher dose of the standard cytokine alone leads to an increased efficacy as compared with the standard dose, reasons should be given why such an increased dosage of the standard cytokine alone might not serve as a comparator in terms of efficacy or why an unfavourable risk/benefit ratio may

be expected from such an approach. Such considerations are particularly relevant, when patients as defined in section 3.1./3.2. are the target population of the study.

4.2.4 Primary endpoint

A difference in the clinically most relevant and therefore primary endpoint must be demonstrated, i.e.

- the number of patients proceeding to and successfully completing autotransplantation (with any reasons why patients do not achieve this goal being listed in detail)

and

- an adequate toxicity marker (which has to be selected according to the toxicity profile of the substances/regimens compared) in the inferior toxicity situation.

4.2.5 Secondary endpoints

The following clinical parameters may be used as secondary endpoints:

- the number of patients suffering serious adverse reactions/complications (WHO grade III/IV infections and clinically relevant bleedings, days in intensive care units, etc.) during engraftment
- the percentage of patients becoming transfusion-independent
- time to ANC >0.5 x 10^9/l and thrombocytes >20 and >50 x 10^9/l with independence from transfusions
- hospitalisation rates and duration (concerning this endpoint, the procedures and directions for hospitalisation or outpatient care should be given *a priori*, particularly when multicentre studies are performed or data from studies are pooled which were carried out at different institutions or in different countries)

Biomarkers will be considered as supportive evidence for efficacy, such as:

- the number of patients achieving or failing minimal $CD34^+$ cell numbers (usually $\geq 2x10^6$/kg, *adopted by the ISHAGE/EBMT Joint Accreditation Committee, JACIE standards D4.132*), optimal $CD34^+$ cell numbers (usually $5x10^6$/kg) or target $CD34^+$ cell numbers (with the latter to be defined by the applicant if different from minimal or optimal $CD34^+$ cell counts)
- median ± range of $CD34^+$ cells in comparator groups
- the number of aphereses or of large volume aphereses necessary and the number of $CD34^+$ cells/kg/apheresis
- possible tests on stem cell quality, purity or contamination by neoplastic cells

4.2.6 Safety parameters

As mentioned for phase II studies, safety parameters should be reported separately for both the phase in which stem cells are being collected and the time after re-infusion of stem cells. Whenever possible, in phase III trials these parameters should be reported on an intention to treat basis:

- standard toxicity parameters
- adverse reactions or side effects of the mobilisation procedure (thromboses, bleedings, central line complications), analysed according to the number and type of aphereses performed
- the number of days with fever and iv-antibiotics

4.2.7 To be reported as post-marketing data

Evaluation may be done by long-term follow up of the groups compared and/or of control groups treated with similar regimens in identical disease situations but without the cytokine. Such data should be reported according to the legal requirements.

- effects on disease-free survival, relapse-free survival, overall survival in both arms or relevant adequately-matched comparator groups
- long-term adverse effects like stimulation of pre-neoplastic/fully neoplastic clones (i.e. myelodysplastic syndromes, acute secondary leukaemias, secondary solid malignancies)
- long-term effects on bone marrow function

These parameters can be considered as supportive evidence for the purity of stem cells collected and transplanted, for the effect of a substance/regimen on the growth of neoplastic cells and for the safety of the procedure.