

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007;357:1083-93.

Supplement: High-dose melphalan treatment modalities (intensive treatment):

After randomization and further assessment of amyloidosis, G-CSF treatment will start with a daily dose of 10 µg/kg in two injections.

Cytapheresis will begin on day 5, and will be pursued until at least  $2 \times 10^6$  CD34+ cells/kg have been collected (or  $10 \times 10^4$  CFU-GM/kg, depending on the practices of each center). As G-CSF may be poorly tolerated in patients with pulmonary or cardiac involvement, these patients will be closely monitored during treatment.

If the first collection is unsuccessful, only one further attempt at G-CSF mobilization may be envisaged. If the second collection fails, the patient's subsequent treatment will be decided by his or her physician, but the patient will nonetheless be retained for analysis in the intensive treatment group.

#### PERIPHERAL STEM CELL MOBILIZATION AND COLLECTION

Mobilization: peripheral stem cell collection will take place in steady state; G-CSF will be administered at a dose of 10 µg/kg/day, from D1 until the last day of cytapheresis.

Cytapheresis will start on Day 5. Two to three blood masses will be treated in each session, with a collection target of at least  $2 \times 10^6$  CD34/kg.

Hypocalcemia is poorly tolerated by patients with amyloidosis, and their calcium intake should therefore be augmented during the period of cytapheresis.

## CARDIAC AMYLOIDOSIS

The cardiomyopathy associated with cardiac amyloidosis is characterized by diastolic dysfunction, while systolic function is often preserved, leading to a ventricular filling defect and to a decline in cardiac output. In such a context, even mild hypovolemia can lead to life-threatening cardiogenic shock.

To reduce this risk, the following precautions should be taken:

- infusion of 1000 ml of normal saline within 12 hours before cytapheresis
- cytapheresis should be performed in an intensive care unit with continuous ECG monitoring and BP measurement every 5 minutes.
- cytapheresis should start at a sampling rate of 40 ml/min while the sampling kit is being primed (corresponding to about 250 ml with the above-mentioned separators). If diastolic pressure falls to less than 5 mmHg, the cytapheresis session should be interrupted and normal saline infused to improve the BP (diastolic pressure >5 mm). Once blood starts to return from the separator to the patient, the sampling rate can be increased to the usual values (50 to 60 ml/min).

- in case of marked cardiogenic edema (ascites or pleural effusion) the fluid overload linked to anticoagulation with ACD-A can be reduced by adding 6000 IU of heparin per 1000 ml of ACD-A and by reducing the anticoagulant/blood ratio to 1/18. It is also necessary to add 1000 IU of heparin to the collection bag during or just after the cytapheresis session.
- autologous plasma should not be used for freezing, but albumin should be used instead (plasma collection leads to hypovolemia and an abrupt decline in BP).
- between two and three blood masses should be cytapheresed.

#### RENAL AMYLOIDOSIS WITH RENAL FAILURE AND ANURIA

The following precautions are necessary to avoid marked fluid overload:

- a dialysis session should be performed in the afternoon before the first cytapheresis session. The patient should remain under fluid restriction (maximum 500 ml/24 hours). Two cytapheresis sessions should take place on the following two days, followed by a dialysis session in the afternoon after the second cytapheresis session. If necessary, two cytapheresis session will be followed by dialysis sessions.
- reduction in the anticoagulant ratio after heparin addition (see *Cardiac Amyloidosis*); between two and three blood masses should be cytapheresed.
- 200 ml of autologous plasma should be collected for freezing (thus reducing fluid overload).

RENAL AMYLOIDOSIS WITH RENAL FAILURE AND PRESERVED

DIURESIS

These patients can undergo cytapheresis in standard conditions.