Therapy of Primary Systemic Amyloidosis

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Primary AL Amyloidosis

- Primary AL amyloidosis is a plasma cell dyscrasia related to multiple myeloma
- An excess production of abnormal immunoglobulin light chains are deposited in vital organs
- These include the kidneys, heart, liver, brain, G.I.T. and bone marrow
- Soft tissue and peripheral nerves are also commonly involved

Primary AL Amyloidosis

- Tissue deposits are in the form of fibrillar amyloid protein which damages the involved organs impairing their function
- Most patients have evidence of a plasma cell neoplasm with monoclonal proteins in the serum and/or urine, and a small but demonstrable plasma cell clone in the bone marrow

Conventional Chemotherapy

- Conventional multiple myeloma-like chemotherapy with oral melphalan and prednisone has median survival of 12-14 months
- High dose melphalan with autologous peripheral stem cell rescue is useful in multiple myeloma resulting in ~22% complete remission rate
- As amyloid is a myeloma variant, high dose melphalan may play an important role in primary amyloidosis

Autologous Stem Cell Transplantation

- Hematological rescue after administration of high dose single agent or combination myelosuppressive chemotherapy
- High dose chemotherapy is given to overcome primary or secondary tumor resistance to conventional doses of cancer chemotherapy
- Re-infusion of autologous stem cells enables the bone marrow to recover from potentially fully myeloablative doses of chemotherapy drugs

Autologous Stem Cell Transplantation

- Chemotherapy should have minimal non-hematological toxicity at conventional doses with dose limiting toxicity at high doses being only hematological
- Doses are escalated up to levels at which non-hematological toxicity develops without the limitation of any hematological toxicities
- At least 1 log (>10 fold) increase in dosage is usually required to overcome either primary or secondary drug resistance

Autologous Stem Cell Transplantation

Alkylating agents are the mainstay of high dose chemotherapy agents:

- Cyclophosphamide can be escalated from about 600mg/m^2 to 6g/m^2 (~10x) when hemorrhagic carditis may develop
- Thiotepa can be escalated from 30mg/m^2 to 900mg/m^2 (up to 30x) and may be best drug available

Autologous Stem Cell Transplantation

Alkylating agents:

- Carboplatin can be escalated from ~400mg/m^2 (AUC6) -> ~1200mg/m^2 (AUC18) (~3x) when nephrotoxicity and neurotoxicity develops
- Cisplatin can be escalated from ~100mg/m^2 to ~200mg/m^2 (~2x) when renal, neurotoxicity and ototoxicity toxicity develops

Autologous Stem Cell Transplantation

Alkylating agents:

- Carmustine can be escalated from ~120mg/m^2 to ~600mg/m^2 (~5x) when irreversible pulmonary toxicity occurs
- Melphalan can be escalated from ~40mg/m^2 to ~240mg/m^2 (~6X) when severe mucositis develops

Autologous Stem Cell Transplantation

Non-alkylating agents: More difficult to use

Topoisomerase II inhibitors:

- Mitoxantrone doses of up to 100mg/m^2 (~3x) have been used but has resulted in irreversible cardiotoxicty and acute myeloid leukemia (11q23 abnormalities)
- Etoposide has been used up to 1.5-2g/m^2 (~6x) but causes severe mucositis, hypotension and nephrotoxicity as well as increased AML risk

High Dose Chemotherapy in AL Amyloid

- Data from Commenzo and Skinner (BU) (Blood 1996), showed very high response with melphalan 200mg/m² followed by autologous stem cell rescue
- Follow-up data (1998) however showed a response of about 65% with significant treatment related mortality especially in patients with cardiac or hepatic disease

Local Experience

- 8 patients (Hematology 2007)
- Peripheral stem cell mobilisation with G-CSF (filgrastim or lenograstim) 5 - 10µg/kg/day (Day -5 to Day 0)
- Stem cell harvest >$2x10^6$/ kg CD34+ cells
- Intravenous melphalan 140-200mg/m^2
- Re-infusion of stem cells after 72 hrs

Results

- 2 patients were alive with stable disease 36 and 102 months after treatment, with an increase in their serum albumin and immunoglobulin levels
- 2 patients died of cardiac amyloid after 24 and 96 months
- 4 patients died from neutropenic sepsis, acute on chronic renal failure or CNS bleeding 13-55 days after high dose melphalan chemotherapy

I.F.M. (France)

- Jaccard et al; NEJM 2007
- Randomized Study: High dose melphalan + ASCT vs standard dose oral melphalan + high dose dexamethasone
- 100 patients (18 – 70 years)
- Median follow-up 3 years
- Median survival 22.2 months (ASCT) versus 56.9 months (M+HDD) (p=0.04)
- High risk patients no difference in OS
- Low risk OS at 3 years 58% vs 80% (NS)
- No advantage for HD melphalan + ASCT

United Kingdom

- Phillip Hawkins (National Amyloidosis Centre at Royal Free, London)
- Age over 55, a large amyloid load on SAP scan, cardiac impairment, G.I.T. bleeding and autonomic neuropathy are major risks for treatment related mortality
- ?ASCT only in low risk patients

United States Recommendation

- Ray Commenzo (MSKCC) (J Natl Compr Canc Netw 2007)
- Patients with limited organ involvement: Melphalan 100-200mg/m2 plus ASCT followed by thalidomide + dexamethasone in patients with persistent plasma cell disease have 77% response
- Thalidomide + dexamethasone alone have 66% response
- Bortezomib and lenalidomide promising in refractory patients

Thalidomide

- Palladini et al (Pavia)
- Thalidomide 100-400mg + dexamethasone (Blood 2005)
- 31 patients failing front line therapy
- 48% response with 19% CR
- M+D plus thalidomide (Ann Hematol 2008)
- 22 patients not fit for ASCT
- 6 cardiac deaths
- 8 haematological responses + 4 cardiac responses

Lenalidomide

- Dispenzieri and Gertz (Mayo) (Blood 2007)
- Lenalidomide with dexamethasone added after 3 months
- 23 patients (13 previously treated)
- 10 progressed prior to dexamethasone
- 10 responders received dexamethasone
- Lenalidomide alone appears inadequate but lenalidomide + dexamethasone encouraging

Bortezomib

- Wechalekar et al (National Amyloidosis Centre at Royal Free) Haematologica 2008
- 20 patients with AL amyloid failing 1-6 lines of therapy
- Bortezomib +/- dexamethasone
- 3 CR and 13 PR
- 8 had significant neurotoxicity

Recommendations

- Ray Commenzo (MSKCC, USA)
- High dose melphalan + ASCT in patients with adequate cardiac, pulmonary or hepatic function
- Solid organ transplant followed by ASCT in cardiac or liver disease should be considered
- Encouraging role for new agents including thalidomide, lenalidomide and bortezomib

Recommendations

- Phillip Hawkins (National Amyloidosis Centre, UK)
- ? Low risk patients
- Jaccard et al (IFM, France)
- Randomized study suggests no role for ASCT

Conclusions

- High dose melphalan with autologous peripheral stem cell rescue may still be feasible in low risk patients
- An acute mortality rates of up to 50% is extremely concerning
- Presence of cardiac, hepatic or renal dysfunction increases risk
- Encouraging role of newer agents eg. IMiDS + proteasome, HDAC and MAPK inhibitors may replace ASCT