Myeloma Management Guidelines

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SUMMARY

The rapid expansion over the last 10-15 years in the our understanding of the initiation and progression of myeloma has directly resulted in the identification of novel targets and new drugs that impact directly on the myeloma cell and indirectly via the microenvironment that is so important in maintaining survival and proliferation of the tumour cell. It has also become very clear that myeloma is a heterogeneous condition that is not amenable to a "one size does not fit all" treatment. The availability of new agents that work through a variety of different molecular mechanisms has allowed us, for the first time ever, to provide risk adapted therapy whilst we move closer toward a targeted therapy approach. The choice of novel agent will depend on concomitant medical conditions and risk factors, disease prognostic factors and patient compliance and convenience. It is also important in the absence of a curative treatment, that individual patient pathways are planned early in the course of the disease to ensure patients are not denied access to active drugs during their treatment journey and that combinations are delivered in an optimal fashion that maximises benefit whilst reducing toxicity. As a result of recent research and development, myeloma patient survival and quality of life have improved significantly as we enter the 21st century.

Epidemiology:

MM is reported to account for approximately 1% of all neoplasms and 12 -15% of all haematological malignancies Greenlee *et al.,* 2000. Various studies in MM have reported diverse incidence rates ranging from 0.9 per 100, 000 to 4 per 100, 000 per year Cartwright *et al.*, 1999b, Finnish Leukaemia Group, 1999, Lenhoff *et al.,* 2000. In England and Wales there are approximately 2,600 cases reported annually Coleman *et al.,* 1999 but the incidence between regions varies for a number of reasons. In African-Americans the incidence is higher than that in Caucasians 9.6 *vs*.1.2 per 100, 000 (Anderson, 1998) and in South Thames, where there is a large Afro-Caribbean population, we have found that the incidence of myeloma is 6.8:100,000 of the population

(Phekoo et al 2004). In recent years there has been an apparent rise in incidence of the disease attributed to increased availability and utilisation of medical facilities and improved diagnostic techniques [Anderson 1998]. The median age at diagnosis has previously been reported at 67 years [Wisloff *et al.,* 1997] and less than 1% of patients are aged < than 40 years (Coleman *et al.,* 1999) which would corroborate the assertion by Soutar *et al.,* (1996) that the continuing rise in incidence is due to improved case ascertainment, especially in the elderly. In our population study the median age was significantly higher at 73 years lending further support to this assertion.

In clinical studies the median survival from the time of diagnosis has, until recently, been unchanged at 3.5 years [Powles, 1997.] The Finnish Leukaemia Group (1998) in their study of an unselected group of myeloma patients up to the age of 70 years reported that 13% were alive after ten years with conventional chemotherapy, the median overall survival being 49 months. Until recently, it has been suggested, only a small proportion of patients (less than 5%) who are eligible are actually entered into trials [Powles *et al.* 1997]. Furthermore, all clinical studies with patients less than 65 years have been performed in single or multi-centre studies [Blade et al, 1998, Powles *et al.,* 1997] and may be effected by referral bias [Ong *et al.,* 1997]. This situation has seen a dramatic reversal with the MRC/NCRI MMIX trial which is the largest myeloma trial ever conducted and is currently undergoing analysis.

Treatment Options:

Real improvements in survival for patients with myeloma had to await the introduction of melphalan in the 1960s' when an increase in life expectancy from approximately six to 24 months was seen. However, response rates for oral melphalan vary between 40-60% and complete remissions are seen in only 5-10% of patients. Combination chemotherapy improved response rates and in some trials improved survival although this advantage was only identified in patients under the age of 65 years. Complete remissions increased from 5% to 30% with the use of high dose melphalan or combination chemotherapy and with dose escalation and autologous haemopoietic stem cell support this rises to 50%.

Single agent melphalan was the first chemotherapy agent to be use in myeloma and it remains an effective chemotherapy drug. Intravenous, intermediate dose melphalan at 25mgs/m^2 in de-novo patients is well tolerated as an out-patient and induces responses in 70- 80% of patients with 37% achieving complete remission [Schey S et al 1998]. Overall survival in this study was 65% at 3 years and progression free survival 51% at 41 months; median progression free survival was 23 months. The Hovon group dose escalated melphalan to 70mgs/m and has reported complete and partial response rates of 18 and 84% respectively. Survival rates are not reported in this study.

Combination chemotherapy has increased complete and partial response rates but there has been no significant improvement in overall survival whilst the ECOG group reporting a randomised study of oral melphalan versus combination chemotherapy showing overall survival to be 32 and 37 months respectively. The Myeloma Trialists' Collaborative Group reviewed 6633 patients' data from randomized trials comparing MP with combination chemotherapy: response rate was significantly higher with combination therapy (60% versus 53.2%, $p<0.00001$), but no advantages on survival were observed. MP was as effective as the best combination in elderly patients and more convenient because of its oral route of administration, a finding confirmed by the MRC MM VII trial. Vincristine, adriamycin and dexamethasone (VAD), is no longer considered the preferred first line therapy for myeloma.

Novel Agents:

Insight into the mechanisms by which soluble factors, such as cytokines, antibodies and small molecules or cell-cell contact with lymphocyte, osteoblasts, osteoclasts or stromal cells induce proliferation, apoptosis or migration of the cell has resulted in a paradigm shift in our approach to treating myeloma. The role of the myeloma microenvironment in producing cytokines and macromolecules that affect the growth and survival of myeloma cells is now also becoming clearer. Outcomes from relapse studies and early results from de novo trials are extremely encouraging showing improved responses and survival compared to conventional chemotherapy.

The combination of melphalan with thalidomide has been investigated in two phase II studies of elderly newly diagnosed patients. In an Italian study, 49 patients older than 65 years were treated with melphalan 4 mg/m2 and prednisone 40 mg/m2 daily on day 1 to 7 every month, combined with continuous thalidomide, 100 mg daily for a total of 6 courses. Seventy-three percent achieved a PR or greater response, with 24% of patients attaining a CR or near-CR; 2 years EFS and OS were 64 and 91% respectively. In a Greek trial, patients older than 75 years were treated with a less dose-intensive approach combining melphalan (8 mg/m2 daily on day 1 to 4) with pulsed dexamethasone (12 mg/m2 daily on day 1-4 and 14-18) and a higher dose of thalidomide (300 mg daily on days 1-4 and 14-18) in 5 week-cycles for up to 9 courses. 72% of patients showed at least a PR and 10% had immunofixation negative CR comparable with the Italian study. Median PFS was 21.2 months and median OS 28.2 months. No significant difference in toxicities were noted despite the differences in treatment schedule and patients' age,: major grade 3-4 adverse events were hematologic toxicity in about 20% of patients, DVT in 18.5% and 9%, neurological manifestation in 8% in both studies.

Two further phase III randomized trials of MP and MPT have been conducted. An Italian study randomized 255 elderly patients (median age 72 years, range 60-85), between treatment with MP or MPT at the same dose as the phase II experience to a total of 6 courses followed by

maintenance treatment of single agent thalidomide. The overall response and CR rates were 76% and 16% in the MPT group, versus 48% and 2% in the MP group. The 2-year EFS in patients treated with the MPT schedule was significantly improved (54% versus 27%, P=0.0006) but no significant difference in 3-years OS was observed (80% versus 64%, P=0.19). This may have been due to the higher proportion of early death in the first 9 months of the study. There was an increased rate of adverse events, principally thromboembolism (12%; reduced from 20% before the introduction of anticoagulant prophylaxis to 3% after), infections (10%) and peripheral neuropathy (8%) in the MPT arm. The IFM group randomization patients aged 65-75 years between 3 arms: MP, MPT and MEL100 with 12 cycles of MP were given in the MP and MPT arms. Higher thalidomide doses were used (up to 400 mg/day) and no maintenance thalidomide therapy was planned. MPT demonstrated a higher rate of CR and VGPR and showed a significant improvement in PFS and OS for the MPT arm compared with standard MP (P<0.001 and P=0.001 respectively) and MEL100 (P=0.001 and P=0.004 respectively). Similar grade 3-4 toxicity for the MPT arm was observed, but at a cost of increased neutropenia, infections, neurological, cardiac and thromboembolic events.

A phase I-II trial of MP in association with escalating doses of lenalidomide (MPR) in newly diagnosed elderly multiple myeloma patients defined the maximum tolerated dose of the combination with lenalidomide of 10 mg daily (day 1-21) plus melphalan 0.18 mg/Kg daily and prednisone 2 mg/Kg daily (day 1-4) every 4 weeks for a total of 9 cycles. 81% of patients showed at least a PR, including 47.6% of patients with at least a VGPR and 23.8% immunofixation negative CR. The 1-year EFS and OS rates were 92% and 100%, compared to the historical MPT control of 78% and 87.4% respectively. No significant differences in response rate and EFS were observed between patients with or without deletion of chromosome 13 or t(4;14). The major side effects neutropenia (52%) and thrombocytopenia (24%). Grade 3&4 non-hematologic adverse events were febrile neutropenia and vasculitis (9.4%); no neurological toxicity was observed and the frequency of thromboembolism was low (4.8%) with aspirin prophylaxis.

Bortezomib has been used in newly diagnosed patients. A Spanish group published the results of a phase I-II study testing the activity of bortezomib combined with MP (VMP) in 60 patients who were at least 65 years old. Overall response rate was 89%, including 43% CR. At 16 months EFS and OS were 83% and 90% respectively, compared to the MP historical control (51% and 62%, P<0.001). Responses were observed in patients with poor cytogenetic prognostic factors. Thrombocytopenia (51%) and neutropenia (43%) were the major grade III-IV hematologic adverse events, while peripheral neuropathy (17%) and infections (16%) were the most common non-hematologic toxicities. Another phase III study of 682 newly diagnosed elderly patients were randomised between MP and VMP. The CR rate was 35% versus 5% (p<0.000001) and the advantage seemed independent of age, renal status or cytogenetic profile. Gastrointestinal, neurotoxicity and fatigue were all more common in the VMP arm. VMP

and MPR are now under investigation in two international phase III trials comparing them with standard MP. A phase 3 study of Bortezomib in combination with both dexamethasone and pegylated liposomal doxorubicin compared with Bortezomib alone [Orlowski 2007] showed a CR + PR response rate of 41% versus 44% (NS) whilst the median duration of response was increased from 7 to 10.2 months. Neutropenia and thrombocytopenia were the major dose limiting toxicities and grade ¾ toxicities were reported in 80% of patients in the combination arm. Bortezomib has also been reported [Davies 2007, Kropf 2007, Berenseon 2006] in small phase I/II studies in combination with cyclophosphamide and melphalan, both orally and intravenously, with combined CR plus PR response rates increasing to 47-78%.

The effect of the combination of thalidomide and bortezomib with oral MP (MPTV) is also under investigation at relapse. Thirty patients at first or second relapse were treated with bortezomib (1.0, 1.3 or 1.6 mg/ m2 on day 1, 4, 15 and 22) plus oral melphalan (6mg/ m2/day) and prednisone (60 mg/ m2/day) from day 1 to 5 and thalidomide 50 mg daily. Each cycle was 35 days long and a total of 6 courses were planned. 43% of patients attained at least a VGPR with 17% immunofixation negative CR. At first relapse CR increased to 36%. Median PFS was 12 months. Toxicities were manageable and this combination is currently under evaluation in a randomized phase III trial in previously untreated patients.

Alkylating agents other than melphalan have been used successfully in the UK for many years. A series of clinical trials performed by the Medical Research Council in the late 20th century, demonstrated the equivalent efficiency of cyclophosphamide to melphalan. Cyclophosphamide also has a favourable toxicity profile compared to melphalan being associated with less profound myelosuppression, a large non-renal component of elimination making it a safer drug for patients with renal impairment and lacking the stem cell toxicity of melphalan, making it safer to use in younger patients destined for transplantation. The MM IX trial of de novo disease compared cyclophosphamide, thalidomide and dexamethasone (CTD) with melphalan and prednisolone (MP) in non-transplant patients and with cyclophosphamide, vincristine, adriamycin and dexamethasone (C-VAD) in transplant candidates. Analysis of this study is ongoing and are eagerly awaited.

A Phase I/II study of Lenalidomide and dexamethasone in combination with liposomal doxorubicin and vincristine in de novo disease, demonstrated a high combined response and CR/nCR rate (75% and 29% respectively) but the maximum tolerated dose of lenalidomdie was 10mgs /day [Baz 2007] Another study by a German group [Knop 2007] used Lenalidomide at a dose of 25mgs in combination with dexamethasone and conventional doxorubicin and achieved a combined CR+PR rate of 87% and a CR and nCR rate of 23% and 60% respectively with less toxicity suggesting that in combination with chemotherapy maintaining the dose of Lenalidomide at 25mgs may induce a better response and toxicity profile.

A number of papers have suggested the presence of t(4;14), t(14;16), t(14;20) and del17p13 on FISH and del 13 on metaphase cytogenetics conferred high risk. In small sub-group analyses both Bortezomib and Revlimid have been shown to be equally as effective for standard and high risk groups.

Targeting poor prognostic groups:

There are a number of poor risk groups identified that include:

1. Renal failure: Bortezomib can be used safely in renal failure and both thalidomide and Revlimid can be used with appropriate dose reductions. Only sub-group analysis of survival data from phase III trials have been conducted and the results of prospective randomised trials need to be evaluated to validate the benefits of these novel agents in renal failure.
2. Poor cytogenetics: Better patient selection using chromosome and molecular markers, and possibly genomics and proteomics, are likely in the future to allow classification of patients who may benefit from specific treatment options. However, the data is derived from retrospective analyses of small phase II trials. Large cohort prospective randomised trials with long-term follow-up are needed to provide more precise prognostic models to stratify patients and validate these findings.
3. Age. Chemotherapy needs to be used with caution in elderly patients because of the increased risk of toxicity, particularly myelotoxicity. There is evidence to suggest that elderly patients are undertreated which may account for their poorer prognosis. The use of the less toxic novel

Recommendations:

Patients should only be treated if they have end-organ damage referable to myeloma or evidence of disease progression. Induction treatment has been developed with the goal of increasing the complete response rate.

Induction Therapy:

- All decisions to treat patients should be predicated on an individual patient basis after a careful and detailed clinical evaluation and investigation. Treatment should then be selected in light of any concomitant medical disorders (e.g. heart failure, MDS, renal impairment).
- Exposure to alkylators and nitroureas should be restricted where possible to patients who are not considered suitable or choose not to receive stem cell transplantation. A

Front-line therapy in transplant candidates

- Thalidomide containing regimens
  - thalidomide + dexamethasone (TD)
  - thalidomide + adriamycin + dexamethasone (TAD)
  - thalidomide + cyclophosphamide + dexamethasone (CTD)

- Bortezomib containing regimens
  - bortezomib + dexamethasone (VD)
  - Bortezomib + melphalan + dexamethasone (VMP)
  - bortezomib + adriamycin + dexamethasone (PAD)

- Lenalidomide containing regimens
  - lenalidomide + dexamethasone (high-dose vs low-dose) LD;Ld)
  - lenalidomide + adriamycin + dexamethasone (RAD)
  - lenalidomide + cyclophosphamide + dexamethasone (RCD)

- Combinations of new drugs
  - bortezomib + thalidomide + dexamethasone (VTD)

Non-Transplant Candidates:

The addition of Thalidomide, Bortezimib or Lenalidomide to an anthracycline increases responses compared to chemotherapy alone but at the expense of increased toxicity

- CTD
- MPT
- MPB/MVP

Choice of Novel agent:

This will depend on a number of factors:

• Antecedent or Risk of DVT	Botezomib
• Antecedent peripheral neuropathy	Thalidomide/IMiD
• Presence of renal Insufficiency	Thalidomide/IMiD/Botezomib
• Distance from Hospital	Thalidomide/IMiD
• Poor patient compliance	Botezomib