Hull and East Yorkshire and North Lincolnshire NHS Trusts Haematology Multidisciplinary Team Guideline and Pathway

Multiple Myeloma

1 BACKGROUND

The Hull and North Lincolnshire Haematology Multidisciplinary team manages patients with haematological malignancies on three sites, Diana Princess of Wales Hospital Grimsby, the Queens Centre for Haematology and Oncology at Castle Hill Hospital Hull and East Yorkshire Hospitals NHS Trust and Scunthorpe Hospital.

Levels of service provided in these organisations is as defined in the NICE guidance "Haematological Cancers: improving outcomes NG47" 25th May 2016.

Low-to-intermediate intensity chemotherapy is delivered in Grimsby, the Queens Centre Castle Hill Hospital and Scunthorpe Hospital.

High-intensity chemotherapy and autologous stem cell transplantation is delivered at the Queens Centre, Castle Hill Hospital.

Allogeneic stem cell transplantation is delivered in the regional transplant centres in Leeds, Nottingham and Sheffield.

The following chemotherapy regimens for multiple myeloma (MM) can be delivered in centres providing low-to intermediate intensity chemotherapy:-

Melphalan, Prednisolone, Thalidomide (MPT).
Melphalan, Prednisolone, Bortezomib (MPV).
Cyclophosphamide, Thalidomide, Dexamethasone attenuated (CTDa).
Melphalan Prednisolone (MP).
Bortezomib Dexamethasone (VD).
Bortezomib, Cyclophosphamide, Dexamethasone (VCD).
Carfilzomib Dexamethasone.
Lenalidomide Dexamethasone (Len Dex).
Ixazomib, Lenalidomide, Dexamethasone.
Bortezomib, Dexamethasone, Panobinostat.
Daratumumab.
Pomalidomide Dexamethasone (Pom Dex).

The following chemotherapy regimens for multiple myeloma (MM) can only be delivered in centres providing high intensity chemotherapy:-

Cyclophosphamide, Thalidomide, Dexamethasone (CTD)
Bortezomib, Thalidomide, Dexamethasone (VTD).
ESHAP.
DT-PACE.
Intermediate-dose Melphalan.
Cyclophosphamide priming chemotherapy.

2 POLICY / PROCEDURE / GUIDELINE DETAILS

Management of Multiple Myeloma (MM)

MM will be diagnosed and managed within the Hull and North Lincolnshire MDT in line with the International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma (Rajkumar et al. 2014) and NICE guideline “Myeloma: diagnosis and management”, Published: 10 February 2016.

The local management of MM will also take account of the following NICE pathways and guidance.

Myeloma pathway. https://pathways.nice.org.uk/pathways/myeloma.

Myeloma: diagnosis and management. Published: 10 February 2016. nice.org.uk/guidance/ng35

Bortezomib monotherapy for relapsed multiple myeloma (TA129). Technology appraisal guidance, published October 2007.

Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228). Technology appraisal guidance, published July 2011.

Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). Technology appraisal guidance, published April 2014.

Carfilzomib for previously treated multiple myeloma (TA457). Technology appraisal guidance, published July 2017.

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). Technology appraisal guidance, published February 2018.

Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). Technology appraisal guidance, published June 2009 Last updated April 2014.

Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). Technology appraisal guidance, published January 2016.

Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). Technology appraisal guidance, published January 2017.

Diagnosis of MM

Myeloma will be diagnosed in line with IMWG criteria. (Rajkumar et al. 2014).

Diagnostic material (blood, bone marrow, skeletal or soft tissue biopsies) is to be sent directly to HMDS, Leeds.

All newly diagnosed cases of myeloma are to be discussed at the network MDT.

Newly Diagnosed MM

Asymptomatic myeloma

Asymptomatic myeloma is defined as myeloma in the absence of end-organ damage (no evidence of myeloma-related cytopenias, renal impairment, hypercalcaemia or skeletal disease), a free light chain ratio of <100, or >0.01, no evidence of myeloma-related skeletal disease on cross-sectional imaging (CT or PET-CT) and <60% plasma cells in the bone marrow.

Multiple Myeloma

MM is defined by the presence of clonal plasma cells in bone marrow (>10%) or a tissue biopsy, monoclonal protein in serum or urine and myeloma-related organ dysfunction ([C] Calcium elevation, [R] Renal insufficiency [A] Anaemia [B] Lytic bone lesions). Rare cases of non-secretory myeloma may be diagnosed in the absence of monoclonal protein.

MM may also be diagnosed in the absence of and myeloma-related organ dysfunction in the presence of any of:-

- Serum free light chain ratio of >100 or <0.01.
- Plasma cell infiltration >60% in bone marrow.
- >1 lytic lesion on PET-CT or whole body CT.

First line-treatment of Multiple Myeloma

Intensive

Patients potentially fit for an autologous-stem cell transplant are treated on an intensive pathway. Fitness for autografting is dependent on the presence of comorbidities, performance status and response to induction chemotherapy. The final decision on fitness for autologous stem-cell transplantation is made by the transplant team in Hull.

Patients potentially fit for an autologous stem cell transplant should be formally referred to the transplant team in the Queens Centre at the earliest opportunity and at the latest before the fourth cycle of induction chemotherapy.

Patients treated intensively should receive a regimen incorporating two novel agents and a steroid such as VTD. Other regimens could include CTD or VD.

A minimum of a partial response is required prior to stem cell mobilisation. Attainment of less than a partial response (50% or less reduction in monoclonal protein) after three cycles of induction chemotherapy should prompt a change in therapy to a non-cross-reacting regimen such as ESHAP or DT-PACE or other therapies accessible according to current NICE guidance.

Non-intensive

Patients defined as unfit for autografting are treated on a non-intensive pathway. Treatment options for this group include MPT, CTDa, MP, VD and MPV. Bortezomib-based regimens should be used in those patients for whom thalidomide-based therapy is inappropriate. Treatment should be continued to at least maximum response, 6 cycles or until unacceptable toxicity or progression occurs.

Second-line therapy

Patients fit for second autograft

Patients relapsing at least 18 months years after an initial autograft should be considered for a second autograft. Reinduction therapy for patients potentially fit for a second transplant is dependent on the prior front-line therapy:-

- Bortezomib naïve patients could receive VD or carfilzomib.
- Patients previously exposed to bortezomib could be treated with a thalidomide-based regimen, ESHAP or DT-PACE.

Patients not fit for second transplant/previous non-intensive patients

Relapsing patients previously treated non-intensively who need further therapy can be considered for either VD, carfilzomib or a thalidomide-based regimen. Frail patients could be treated with single agent cyclophosphamide, steroid monotherapy or palliatively.

Third-line therapy and beyond

Patients in second-relapse and beyond should be assessed for further therapy in line with their wishes and expectations. Options for therapy include Len Dex, ixazomib/lenalidomide/dexamethasone, bortezomib/panobinostat/dexamethasone and thalidomide-based regimens.

Fourth-line therapeutic options could include Pom Dex and daratumumab.

Patients relapsing after or unresponsive to proteasome inhibitors and lenalidomide have a poor prognosis and consideration of palliative and supportive care should be made for this patient group. The optimum course for any patient is dependent on the nature of their disease and the wishes and expectations of the patient.

Clinical Trials

All patients should be considered for, and offered entry into, clinical trials where available.

Patients relapsing after proteasome inhibitor and lenalidomide therapy have a poor prognosis and should be offered entry into a clinical trial, if available and appropriate for the individual, either locally or regionally.

Allogeneic Transplantation

Patients identified as potential candidates for allogeneic transplantation should be discussed at the earliest opportunity with the transplant team at either Leeds or Sheffield.

Identifying a group of patients with myeloma who may benefit from this procedure is difficult but may include relatively young, fit patients identified as having high risk-disease. High-risk disease may include the presence of adverse cytogenetic/molecular features at presentation, a poor response to induction chemotherapy and early relapse following autologous stem cell transplantation.

Supportive Care

All patients with MM should be offered bisphosphonate therapy with either zoledronic acid or a bisphosphonate for at least 2 years after diagnosis. Bisphosphonate therapy can be discontinued after 2 years assuming the presence of an ongoing

remission but should be reintroduced at relapse. Patients should be counselled about the risk of osteonecrosis of the jaw and seek a dental review prior to initiation of bisphosphonates in the absence of a recent dental consultation.

Patients receiving thalidomide or lenalidomide in combination with corticosteroids should be risk-assessed for their risk of treatment related venous thromboembolism (VTE). High-risk patients could include those with previous VTE, reduced mobility or other risk-factors for VTE and should receive thromboprophylaxis with low molecular weight heparin. All other patients should receive aspirin as thromboprophylaxis.

Other aspects of supportive care should be in-line with BCSH guideline on supportive care (Snowden et al. 2011).

Management of skeletal complications

Suspected, or proven, spinal cord compression associated with MM should be managed in-line with the network metastatic spinal cord compression pathway.

For patients with known MM radiotherapy is the treatment of choice for spinal cord compression.

Patients with MM-related skeletal disease in need of surgical review should be referred to the network bone metastases MDT for planning and supervision of orthopaedic care.

For patients with spinal disease with poorly controlled pain consideration should be given to referral to the regional vertebroplasty MDT depending on the radiological appearances and could also be considered for palliative radiotherapy.

Palliative care services

All MM patients will have a named key-worker who will undertake a holistic needs assessment and provide support and advice based upon this.

Referral to hospital or community palliative care services should be considered for all myeloma patients but especially for those relapsing after two or three lines of therapy, those unfit for intensive chemotherapy and those with specific palliative care needs.

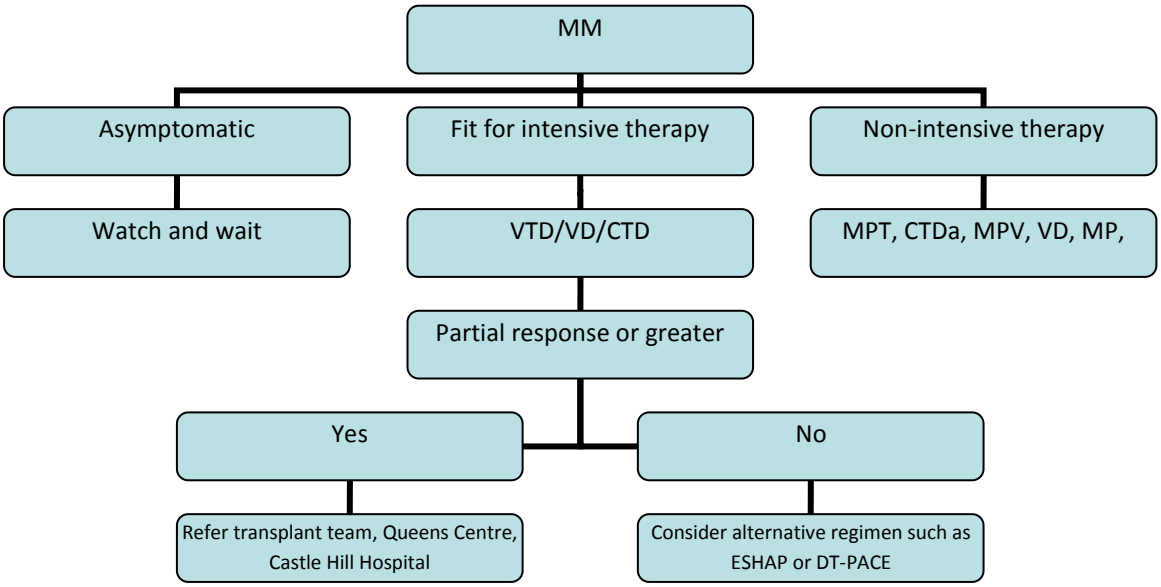
Plasmacytomas

Patients with plasmacytomas should be managed in line with the BCSH plasmacytoma guideline (Soutar et al. 2004), and also BCSH imaging guidelines (Chantry et al, 2017).

All patients with a suspected solitary soft-tissue or bone plasmacytoma should undergo a bone marrow aspirate and biopsy and a PET-CT scan to exclude MM.

Radical radiotherapy is the treatment of choice for isolated plasmacytomas.

Patient Pathway, newly diagnosed multiple myeloma



3 PROCESS FOR MONITORING COMPLIANCE

Compliance will be audited within the MDT audit programme.

4 REFERENCES

- Hull and North Lincolnshire Haematology MDT operational policy September 2017.
- Haematological cancers: improving outcomes. NICE guideline [NG47] Published date: May 2016.
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