bjh guidelines

Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline

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Scope

The objective of this guideline is to provide healthcare professionals with clear guidance on the anti-myeloma management of patients with newly diagnosed multiple myeloma. In all cases, individual patient circumstances may dictate an alternative approach.

Methodology

This guideline was compiled according to the BSH process at https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature Review

Recommendations are based on a review of the literature using Medline, PubMed, Embase, Central, Web of Science searches from the beginning of 2013 up to July 2019. The following search terms were used:

myeloma; plasma cell leukaemia;

AND

risk; prognosis; cytogenetics; FISH; PCR; molecular; imaging; response; residual disease

OR

[chemotherapy; autologous; autograft; HDT/ASCT; allogeneic; allograft; stem cell; bone marrow; cord blood; haploidentical; tandem transplant; bortezomib; carfilzomib; ixazomib; melphalan; thalidomide; lenalidomide; pomalidomide; cyclophosphamide; dexamethasone; prednisolone; doxorubicin; bendamustine; immunotherapy; daratumumab; PDL1 inhibitor; CAR-T; frail; elderly; renal failure; renal impairment; kidney disease; maintenance; consolidation

AND

survival; outcome; relapse; progression; remission; response; residual disease; mortality; morbidity; side effects; adverse events; complication; neuropathy; thromboembolism; infection; quality of life; cost-effective]

Review of The Manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haematology Oncology Task Force, the BSH Guidelines Committee and the Haematology Oncology sounding board of BSH. It was also on the members section of the BSH website for comment. It has also been reviewed by UK Charity Myeloma UK. These organisations do not necessarily approve or endorse the contents.

Diagnosis and Investigations

Patients with suspected myeloma should be investigated using the tests listed in Table I. A bone marrow biopsy should be undertaken in patients in whom there is a clinical concern for end organ damage and/or those with a significantly elevated monoclonal protein (M-protein).

The monoclonal protein should be quantified by densitometry of the monoclonal peak. Quantification of monoclonal immunoglobulin (Ig) A by electrophoresis can be complicated by migration into the beta region. International Myeloma Working Group (IMWG) guidance recommends that

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for IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred.[1] NICE guidance now recommends the use of serum free light chains (SFLC) rather than urinary Bence Jones protein (BJP), and studies have validated this.[2] SFLC replaces BJP in these guidelines, although it is noted that BJP may still be required for some clinical trials. Urine albumin:creatinine ratio along with troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be a useful screening tool for detecting amyloid.

Skeletal survey has been replaced by cross-sectional imaging, including low-dose, whole-body computed tomography (CT), or ideally functional imaging such as computed tomography-positron emission tomography (CT-PET) or diffusion weighted whole body magnetic resonance imaging (MRI). Focal imaging (e.g., dedicated MRI scan of the spine and pelvis, or plain films of long bones) should be performed to look at specific sites in more detail if required. Imaging in myeloma is discussed in detail in recent UK and international guidelines.[3,4]

All diagnoses should be reviewed at a multidisciplinary team (MDT) meeting.

Table I. Initial investigations for patients with suspected and confirmed myeloma.

Screening tests	FBC
	Urea & creatinine
	Calcium
	Immunoglobulins & serum electrophoresis
	Serum free light chains
Tests to establish diagnosis	Bone marrow aspirate & trephine biopsy with plasma cell phenotyping*
	Immunofixation of serum
	Imaging – PET-CT, WB-MRI (diffusion weighted preferably) or low dose WB-CT.
	(See BSH guidelines imaging in myeloma)
Tests to estimate tumour burden and prognosis	FISH Analysis for t(4;14), t(14;16), t(11;14), 17p−, 1q+, 1p−
	Consider testing for t(14;20) and hyperdiploidy
	β2 microglobulin,
	LDH
	Albumin

FBC, full blood count; PET-CT, positron emission tomography CT scan; WB-MRI, whole body MRI scan; WB-CR, whole body CT scan; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase. *Plasma cell phenotyping may be performed by flow cytometry or immunohistochemistry on trephine biopsy sections. When estimating the percentage plasma cell burden, the highest value obtained from either bone marrow aspirate or trephine should be used.

Diagnostic Criteria

Myeloma should be diagnosed using the 2014 IMWG updated criteria.[5] Table II shows the diagnostic criteria for myeloma, smouldering (asymptomatic) myeloma and monoclonal gammopathy of undetermined significance (MGUS).

Table III. Myeloma-defining events adapted from International Myeloma Working Group Updated Criteria.[5]

Myeloma-defining event
[S] ≥60% plasma cells in marrow
[LI] Involved:uninvolved light chain ratio ≥100* (provided the involved light chain is >100 mg/l)
[M] 2 or more focal lesions on MRI (>5 mm in size)
[C] Hypercalcaemia: (>2·75 mmol/l or >0·25 mmol/l higher than upper limit of normal)
[R] Renal insufficiency: (serum creatinine >177 μmol/l or creatinine clearance <40 ml/min†)
[A] Anaemia: Hb <100 g/l or 20 g/l below lower limit of normal
[B] 1 or more lytic bone lesion on X-ray, CT or PET/CT‡ (>5 mm in size)

*i.e. Kappa:Lambda ratio ≥100 or ≤0·01.
†Creatinine clearance measured or estimated by validated equations.
‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

Table II. Diagnostic criteria for myeloma, smouldering myeloma and MGUS. Adapted from International Myeloma Working Group Updated Criteria.[5]

Myeloma	Smouldering myeloma	Non-IgM MGUS†
Both criteria must be met: 1. Clonal bone marrow plasma cells* ≥10% or biopsy proven plasmacytoma. 2. One or more myeloma-defining events (see Table III).	Both criteria must be met: 1. Serum M-protein (IgG or IgA) ≥30 g/l or urinary M-protein >500 mg/24 h and/or clonal bone marrow plasma cells 10–60% 2. Absence of myeloma-defining events or amyloidosis	All three criteria must be met: 1. Serum M-protein (non-IgM) <30 g/l 2. Clonal bone marrow plasma cells <10% 3. Absence of end organ damage that can be attributed to the plasma cell proliferative disorder (e.g. CRAB features, amyloidosis)

*Clonality should be established by showing κ/λ-light chain restriction on immunophenotyping, cytometry, immunohistochemistry or immunofluorescence. If there is discrepancy between the plasma cell percentage in the aspirate and the trephine biopsy the higher value should be used.
†Three variants of MGUS are now defined in the IMWG classification: non-IgM MGUS, light chain MGUS and IgM MGUS. Light chain MGUS requires no immunoglobulin heavy chain on immunofixation, abnormal FLC ratio (<0·26 or >1·65) with increased level of the appropriate involved light, urinary M-protein <500 mg/24 h along with criteria 2 and 3 from non-IgM MGUS. IgM requires serum monoclonal IgM protein <30 g/l, <10% lymphoplasmacytoid cells in bone marrow and no features suggestive of an underlying lymphoproliferative disorder.

Table III summarises myeloma-defining events. The latest guidance reflects a number of changes compared to the previous 2003 criteria.[6]

End organ damage is no longer required to diagnose myeloma. Three biomarkers have been added to the myeloma-defining events, each of which is associated with an approximately 80% probability of the development of CRAB features (hypercalcaemia, renal impairment, anaemia and bone disease). These biomarkers (≥60% clonal plasma cells in the bone marrow, involved:uninvolved light chain ratio ≥100 and ≥2 focal lesions on MRI) are referred to as the SLiM criteria. Studies have shown the rate of progression to myeloma within 2 years is approximately 95%[7,8], 80%[7,9] and 70%,[10,11] respectively. Patients with a solitary focal lesion on MRI or equivocal findings should undergo interval imaging.[4]

The 2003 criteria did not specify the percentage of clonal bone marrow cells required for a diagnosis of symptomatic myeloma. Current guidance confirms 10% clonal plasma cells or biopsy-proven plasmacytoma is required. Current guidance also clarifies that the presence of osteolytic bone lesions >5 mm seen on CT or PET-CT (and not on skeletal radiography) is consistent with a myeloma-defining event. Increased uptake on PET-CT alone, without a corresponding lytic lesion, is insufficient to be a myeloma-defining event, but is associated with an increased risk of progression to myeloma.[5] If there is doubt regarding equivocal or small lucencies (<5 mm), repeat imaging should be performed. Bone lesions should be biopsied if there are concerns they may represent bony metastases from concurrent malignancies. Osteoporosis with compression fractures is no longer a myeloma-defining event.

Criteria regarding renal failure have changed, with creatinine clearance <40 ml/min added as a myeloma-defining event. The criteria now also specify that only renal failure due to light chain cast nephropathy (biopsy proven or presumptive) is a myeloma-defining event. SFLC >500 mg/l is suggestive of cast nephropathy,[12] so renal biopsy should be considered in those patients with SFLC <500 mg/l.[5] Monoclonal proteins can cause other renal pathology (e.g., AL amyloidosis or monoclonal immunoglobulin deposition disease) in patients who do not meet the criteria for myeloma. Such cases are termed monoclonal gammopathy of renal significance.[13]

To be classed as a myeloma-defining event, CRAB events should be due to underlying myeloma and, if unclear, appropriate investigations should be performed to confirm this.

Symptomatic hyperviscosity, amyloidosis and recurrent bacterial infections[1] have been removed from the list of myeloma-defining events in the current guidelines, but may still require treatment.

Diagnostic criteria for other related plasma cell dyscrasias, including solitary plasmacytoma with or without minimal bone marrow involvement, systemic AL amyloidosis and POEMS Syndrome can be found in the IMWG updated criteria for the diagnosis of myeloma.[5]

Cytogenetic Abnormalities

Cytogenetic analysis should be undertaken by interphase FISH (fluorescence *in situ* hybridization) on CD138-selected bone marrow cells. The bone marrow material used should be part of the first aspirate pull wherever possible.[14] Table IV lists the cytogenetic abnormalities found to be of prognostic significance in newly diagnosed myeloma.[15]

Whilst t(11;14) is listed as standard risk, recent analysis of the Myeloma XI trial suggested patients with hyperdiploidy and no adverse lesions had superior outcomes compared to those with t(11;14).[16] Early data suggests t(11;14) is a predictive biomarker for response to the BCL2 inhibitor venetoclax.

t(4;14) is a poor risk marker, although the poor risk can be (partly) overcome by bortezomib-based therapy.[17] The poor prognostic impact of del(1p) has mainly been described in patients treated with autologous stem cell transplantation.[18] The number of extra copies of 1q is relevant; patients with amplification of 1q (four or more copies) having a poorer prognosis.[16,19] Del(13q) detected by FISH is no longer considered an independent prognostic factor.[20-22]

There is a lack of consensus internationally as to the percentage cut-off levels which should be used to signify a positive FISH result. The French group (IFM) suggested 60% was required for clinical significance in del(17p), although this has not been replicated in other studies, and sub-clonal *TP53* copy number abnormalities have recently been shown to be associated with prognosis.[23] The European Myeloma Network suggested 10% for translocations and 20% for copy number abnormalities.[14] Less than 20% has been clearly associated with inferior outcome in the UK MRC Myeloma IX and XI trials. Smaller sub-clones may carry prognostic relevance, but data are currently limited.

UK MRC Myeloma IX and XI studies found an association between the number of adverse cytogenetic lesions present and progressively shorter survival.[16,20]

Staging Systems

The International Staging System (ISS) defines three prognostic categories (Table V). The criteria reflect tumour

Table IV. Prognostic significance of cytogenetic abnormalities in newly diagnosed myeloma.

Standard risk		High risk	
Cytogenetic abnormality	Prevalence (%)	Cytogenetic abnormality	Prevalence (%)
t(11;14)*	15	t(4;14)	15
t(6;14)	5	t(14;16)	2–3
Hyperdiploidy	50	t(14;20)	1
		17p−	10
		1p−	10
		1q+	35–40

*t(11;14) listed as standard risk although some studies suggest the outcome for this group is inferior to those patients with hyperdiploid.[16]

Table V. International Staging System (ISS) for multiple myeloma. Adapted from Greipp 2005.[24]

Stage	I	II	III
Criteria	Serum β2 microglobulin <3·5 mg/l AND Albumin ≥35 g/l	Not fitting criteria for stage I or III	Serum β2 microglobulin ≥5·5 mg/l (irrespective of albumin)

burden and renal function (Beta-2 microglobulin) along with performance status (albumin). The ISS was initially developed in 2005.[24] As such, the median overall survival (OS) associated with each stage (62 months vs. 44 months vs. 29 months) is out-dated. However, more recent studies have confirmed the prognostic significance of ISS in the era of novel agents[25] and at relapse.[26]

The Revised-ISS (R-ISS) combines the traditional ISS with presence of high-risk cytogenetics (del(17p), t(4;14) or t(14;16)) or elevated serum lactate dehydrogenase (LDH).[27] Data were pooled from 4,445 patients with newly diagnosed myeloma enrolled onto 11 international multicentre trials, 95% treated with novel agents. Three risk groups are defined, as shown in Table VI.

Other Prognostic Factors

In addition to the cytogenetic abnormalities discussed above, various recurrent genetic mutations have been associated with a poor prognosis in myeloma—for example, in *CCND1*, *ATM* and *TP53*.[15,28] The National Genomic Test Directory (https://www.england.nhs.uk/publication/national-genomic-test-directories) specifies the genomic tests commissioned for myeloma in the UK. Bi-allelic loss of *TP53* [i.e., del(17p) plus *TP53* mutation, seen in ~30% of del(17p)] has a significantly reduced OS.[28] Gene Expression Profile signatures are also predictive of poor prognosis but are currently used only in the context of clinical trials.[29] Plasma cell leukaemia (defined as 20% circulating plasma cells or a total plasma cell count in peripheral blood of at least 2×10^9/l) remains a poor prognostic factor,[30] as does detection of low levels of circulating plasma cells by flow cytometry.[31] Imaging studies can provide prognostic information; the presence and number of ^{18}F fluorodeoxyglucose (FDG)-avid lesions on PET scanning at baseline and at response to treatment has the most data in this regard at the present time.[32]

Recommendations

Investigations should be based on the tests listed in Table I. (1C)

Serum free light chain analysis should be used to investigate monoclonal light chains rather than urinary Bence Jones protein. (1B)

Renal biopsy should be considered if SFLC <500 mg/l and myeloma is being considered as the cause of renal impairment. (1C)

Cross-sectional imaging, ideally functional (i.e., PET-CT or diffusion weighted whole body MRI), should be used. Skeletal survey should not be used to assess bone disease in myeloma. (1B)

Patients With One Solitary Focal Deposit On MRI Should Have An Interval Scan. (2C)

Urine albumin:creatinine ratio along with troponin and NT-proBNP can be a useful screening tool for detecting amyloid. (2C)

IMWG 2014 diagnostic criteria should be used for staging. (1A)

All cases of newly diagnosed myeloma should be discussed at an MDT meeting. (1C).

Cytogenetic analysis using interphase FISH on CD138-selected cells should be undertaken on all patients at diagnosis. (1A)

Samples should be probed for t(4;14)(p16;q32), t(14;16)(q32;q23), t(11;14)(q13;q32), 17p−, 1q+, 1p− and testing considered for t(14;20)(q32;q11) and hyperdiploidy. (1B)

Table VI. Revised International Staging System (R-ISS). Adapted from Palumbo 2015.[27] Median survival data are based on combined results from 11 international multicentre trials.

Stage	I	II	III
Criteria	ISS stage I AND standard risk cytogenetics* AND normal LDH	Not fitting criteria for stage I or III	ISS stage III AND high-risk cytogenetics† or high LDH‡
Median PFS	66	42 months	29 months
Median OS	Not reached	83 months	43 months
5 year OS	82%	62%	40%
Median OS in transplant based regimens	Not reached	88 months	42 months
Median OS in non-transplant based regimens	66 months	70 months	41 months

*Standard risk cytogenetics by FISH: the absence of high-risk abnormalities.

†High-risk cytogenetics FISH defined as del(17p) and/or t(4;14) and/or t(14;16)

‡High LDH defined as above upper limit of normal for local laboratory.

Cytogenetic abnormalities found in >20% of cells should be considered significant. The significance of smaller clones is not clear. (2B)

Revised ISS should be calculated on all newly diagnosed patients. (1A)

Principles Affecting Choice of Initial Treatment

Survival: Direct and Surrogate Markers

Overall survival is the preferred outcome measure for assessing efficacy, using direct comparisons from Phase 3 trial data where possible. Progression-free survival (PFS) and response rate (RR) can be used as surrogate markers, although caution should be employed in their interpretation. Treatment crossover in trials at progression means that a PFS advantage even in the absence of OS difference may still indicate a benefit from a treatment option; in this context, PFS2 (progression-free survival on the next line of treatment) can provide useful data.[33] Increasingly, sustained Minimal Residual Disease (MRD) negativity is seen as a strong surrogate marker for long-term outcome.[34]

Adjustment for Frailty

Myeloma predominantly affects an elderly population, many of whom are excluded from clinical trials; hence, there can be less certainty about the benefits of treatments and effects on quality of life in this group. Toxicities can be considerable, and dose modification is often necessary. Higher doses of corticosteroids[35] and discontinuation due to adverse events[36] are associated with worse overall survival in this population. Conversely, fitter older patients may receive inappropriate dose reductions if based solely on age.

Evaluation of frailty was traditionally based on age and subjective clinician assessment. More recently, objective fitness scoring systems have been evaluated to estimate prognosis and guide dosing.[37-41] The IMWG score is based on age, the Charlston Comorbidity Index and cognitive and physical conditions, while the UK Myeloma Risk Profile (UK-MRP) uses patient and disease factors.[42] Prospective trial-based testing of these systems is ongoing, and consensus on their use has not yet been reached.

Transplant Eligibility

As discussed below, autologous stem cell transplantation (ASCT) is recommended for younger, fitter patients. There is no formal definition of transplant eligibility and age alone is a poor indicator. Selected patients over the age of 70 may be suitable for ASCT with a low risk of mortality (3–5%). Transplant scoring systems can be used to assess fitness objectively and formal tests of cardiac, lung and renal function performed, although these are not currently standardised.

Side Effects and Comorbidities

A full discussion of side effects and dose reductions is beyond the scope of this guideline, but these have a significant bearing on drug choice and dosing. The Summary of Product Characteristic datasheets should be referred to.

Patient and Clinician Preferences

Patient preferences, including duration of therapy, and practical issues such as the need to travel to a day unit for parenteral treatments are important considerations, especially in the frailer patient population where quality of life as well as OS is important. Local familiarity with regimens can play an important role.

Drug Access and Funding

Licensing and funding varies between countries and regions, and will change over time.

Response Assessment

The criteria for assessment of response continue to evolve and are defined based on paraprotein, bone marrow and imaging responses as: Stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minimal Response (MR), Stable Disease (SD) and Progressive Disease (PD), with the more recent inclusion of MRD-based assessments by flow cytometry or sequencing and imaging.[1] Outside of a clinical trial, light chain assessments can be made by SFLC assay rather than urine BJP quantification.[2] Future trials will explore using MRD and functional imaging responses, but these are not currently used to make routine treatment decisions.

Drug Treatments for Myeloma Patients

This section discusses choice of drug treatment for newly diagnosed myeloma patients. Treatment decisions should be made within an MDT context, and may involve supportive care, surgery and radiotherapy, although these areas are not covered within these guidelines. The aim of treatment for all patients is to maximise the depth and duration of response while minimising toxicity in order to lengthen survival, improve quality of life, alleviate symptoms and prevent further organ damage. Drug regimens referred to in the text are listed in Table VII.

Proteasome Inhibitors

Proteasome inhibitors (PIs) act by altering the degradation of proteins essential for cell cycle and growth.[43] The first in class, bortezomib, was originally given on an intravenous, biweekly schedule, but appears to be equally efficacious with

Table VII. Abbreviations of chemotherapy regimens referred to in the text.

CRD	Cyclophosphamide, lenalidomide, dexamethasone
CTD	Cyclophosphamide, thalidomide, dexamethasone
Dara	Daratumumab
DT-PACE	Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide etoposide
KCD	Carfilzomib, cyclophosphamide, dexamethasone
KCRD	Carfilzomib, cyclophosphamide, lenalidomide, dexamethasone
MP	Melphalan, prednisolone
MPR	Melphalan, prednisolone, lenalidomide
MPT	Melphalan, prednisolone, thalidomide
PAD	Bortezomib, doxorubicin, dexamethasone
RD	Lenalidomide, dexamethasone
TD	Thalidomide, dexamethasone
VAD	Vincristine, doxorubicin, dexamethasone
VAMP	Vincristine, doxorubicin, methylprednisolone
VBMCP/ VBAD	Vincristine, carmustine, melphalan, cyclophosphamide, prednisone, / vincristine, carmustine, doxorubicin, dexamethasone
VBMCP/ VBAD/B	Vincristine, carmustine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, dexamethasone, bortezomib
VCD	Bortezomib, cyclophosphamide, dexamethasone
VCP	Bortezomib, cyclophosphamide, prednisolone
VCRD	Bortezomib, cyclophosphamide, lenalidomide, dexamethasone
VD	Bortezomib, dexamethasone
VMCP/ BVAP	Vincristine, melphalan, cyclophosphamide, prednisone, vincristine, carmustine, doxorubicin, prednisone
VMP	Bortezomib, melphalan, prednisolone
VP	Bortezomib, prednisolone
VRD	Bortezomib, lenalidomide, dexamethasone
VTD	Bortezomib, thalidomide, dexamethasone
VTP	Bortezomib, thalidomide, prednisolone
VAMP	Vincristine, doxorubicin, methylprednisolone

reduced peripheral neuropathy when given weekly and subcutaneously.[44-47] A biweekly schedule may be used as initial therapy to try to achieve rapid tumour control in highly proliferative disease or with cast nephropathy-induced acute kidney injury.

Carfilzomib is a second-generation PI with irreversible proteasome binding which has significant efficacy but higher rates of cardiac toxicity.[48] Carfilzomib is given intravenously, and dosing schedules vary: 70 mg/m^2 once weekly is better tolerated, with improved efficacy compared to 27 mg/m^2 twice a week in the relapsed setting,[49] but optimal dosing remains to be determined in the frontline setting. The oral PI ixazomib has limited data in the first line setting at this time.

Immunomodulatory Drugs

Immunomodulatory drugs (IMiDs) are oral agents that cause myeloma cell apoptosis primarily by interaction with cereblon. Mechanisms of action include degradation of the transcription factors IKZF1 and IKZF3,[50] and immune modulation.[51] The first drug in class, thalidomide, shows clinical efficacy, but is associated with high rates of venous thromboembolism (VTE) when used in combination with corticosteroids,[52,53] as well as tremor, neuropathy and constipation. The newer agents, lenalidomide and pomalidomide, have a lower VTE risk and are better tolerated, but have a higher incidence of myelosuppression, often requiring growth factor support.[54] All IMiDs require risk-stratification and prophylaxis for VTE, as well as a pregnancy-prevention programme due to their potential teratogenicity.

Corticosteroids

These remain a key part of myeloma therapy, with oral dexamethasone and prednisolone being the two most widely used in UK practice. Steroid toxicity can be underestimated, and doses should be reviewed and reduced if possible with long-term use. There are emerging data indicating that steroids can be stopped once patients enter a maintenance phase of treatment with equivalent PFS and OS.[55] Once weekly dosing rather than four-day blocks during initial therapy is associated with lower toxicity and mortality.[35] Higher dose treatments may be given in patients presenting with highly proliferative disease or with cast nephropathy-induced acute kidney injury.

Alkylating Agents

Alkylating agents (e.g., melphalan, cyclophosphamide) may be used in combination with other agents. The doses used are suitable for outpatient regimens, although myelosuppression and mucositis can still occur. More potent cytotoxic chemotherapy combinations such as DT-PACE are sometimes used in aggressive disease.

Monoclonal Antibodies

Monoclonal antibodies, particularly the anti-CD38 antibody daratumumab, deepen response in combination with both IMiD and PI-based chemotherapy and are likely to be adopted in frontline regimens. Toxicities are manageable, but include first dose infusion reactions, interference with blood grouping and interpretation of low-level IgG monoclonal proteins.[56] Other agents, including isatuximab (anti-CD38) and elotuzumab (anti-SLAMF7), have limited data in the first line setting.

Selection of Treatment Combinations

PI/corticosteroid-based Backbone

In direct comparisons, PI-based induction regimens with bortezomib or carfilzomib give greater RR, PFS and, in some

trials and meta-analyses, OS benefit compared to non-PI-based regimens.[57-61] The majority of first line studies have used bortezomib in various combinations in both the transplant eligible (TE) (Table VIII)[59,60,62-64] and non-transplant eligible (NTE) contexts (Table IX).[57,65-68]

Carfilzomib has been tested widely in TE patients (Table X).[69-73] At the time of writing, these data are predominantly in abstract form, with OS data not mature. However, response rates and PFS are all at least as good as with bortezomib-based regimens. Cardiac risks have been highlighted, but the safety profile is acceptable in a younger population. In contrast, data in NTE patients (KMP vs. VMP) have not shown an RR or PFS advantage over bortezomib.[74]

Addition of Third Drug To PI/corticosteroid Therapy

The addition of a third agent often deepens response, although this has not always translated into a survival advantage. The addition of an IMiD increases RR in both the TE and NTE setting, although in direct comparisons, the addition of thalidomide to PI/steroid combination has not shown a survival advantage.[68,75,76] Although VRD has not been directly compared to other bortezomib-based combinations in Phase 3 trials, a retrospective analysis did indicate a survival advantage with VRD over VCD or VD,[77] and single-arm Phase 2 trial data show RR, PFS and OS at least as good as VTD, making this an attractive, well-tolerated option in both TE and NTE patients.[57,63,78] As noted above, VRD is clearly superior to RD for PFS and OS in the large SWOG trial,[57] and a reduced dose protocol (RVDlite) is well-tolerated in older patients, making this a preferred, well-tolerated treatment option.[67]

Alkylating agents are an alternative option for patients who cannot receive an IMiD. VCD can be used for TE patients, although RR is lower than with VTD.[79] PAD is another effective combination that may be used in fitter patients, although its myelosuppressive nature is a drawback.[64,80,81] Melphalan is contra-indicated in TE patients due to the risk of impaired stem cell harvest.

Table VIII. TE regimens: Bortezomib-based induction regimens.

	After Induction			After ASCT/consolidation					
Regimen (*n*)	ORR (≥PR)	CR rate	MRD−	ORR (≥PR)	CR rate	MRD-negative	PFS	OS	Trial/Group name
VTD (241)	93%*	19%*		93%*	38%*		34% at 10 years*	60% at 10 years*	GIMEMA-MMY-3006[59,195]
TD (239)	79%	5%		84%	23%		17% at 10 years	46% at 10 years	
VTD (130)	85%	35%*			57%		52 m*	128 m†	GEM05MENOS65[60,196]
TD (127)	62%	14%			40%		28 m	99 m	
VBMCP/ VBAD/B (129)	75%	21%			48%		32 m	93 m	
VTD (170)	92%*	13%†							IFM2013-04[79]
VCD (170)	83%	9%							
VRD (34)	94%	58%	16% [a]	93%	70%	54%[1]	77% at 3 years	100% at 3 years	IFM2008[63]
VRD (458)	85%	39%	35% [b]	83%	49%	54%[2]			GEM2012MENOS65[78]
VCD (251)	78%†	8%							GMMG MM5[64]
PAD (251)	71%	4%							
VD (240)	79%*	6%*		80%†	16%*	NR	36 m†		IFM2005-01[197]
VAD (242)	63%	1%		77%	9%		30 m		
PAD (413)	78%*	7%*		88%*	21%*	NR	34 m*	91 m†	HOVON-65/GMMG-HD4[80]
VAD (414)	54%	2%		75%	9%		28 m	82 m	
VTD-Dara (543)				93%	39%*	64%* [c]	93% at 18 m*		CASSIOPEIA[87]
VTD (542)				90%	26%	44%	85% at 18 m		
VRDAuto (350)				98%	59%*	79%* [d]	50 m*	81 m†	IFM2009[105]
VRDCons (350)				97%	48%	65%	36 m	82 m	
VRD (42)	73%	24%					83% at 1 year		EVOLUTION (Phase 2)[198]
VCD (33)	63%	22%					93% at 1 year		
VCRD (48)	80%	25%					86% at 1 year		
VCDmod (17)	82%	47%					100% at 1 year		

Post-ASCT protocols varied, with tandem auto, consolidation and maintenance treatments given depending on trial protocol. Comparison of survival data between trials should be viewed with caution.

MRD sensitivity.

[a]2×10^{-6}, [b]3×10^{-6}, [c]1×10^{-5}, [d]1×10^{-4}.

*Significant difference, $P < 0{\cdot}05$.

†Not significant. Where not indicated, statistical differences were not reported.

Table IX. NTE regimens: bortezomib-based.

Regimen (*n*)	ORR (≥PR)	CR rate	MRD negative	PFS	OS	Trial/Group name
VRD (264)[a]	82%	16%		43 m*	75 m*	SWOG S0777[57]
RD (261)	72%	8%		30 m	64 m	
RVDlite (50)	86%	44%		35 m	(not reached)	RVDLite (Phase 2)[67]
VMP (344)	71%*	30%*		22 m*	56 m*	VISTA[61,82]
MP (338)	35%	4%		15 m	43 m	
VD (168)	73%}	3%}		15 m}	50 m}	UPFRONT[68]
VTD (167)	80%}†	4%}†		15 m}†	52 m}†	
VMP (167)	70%}	4%}		17 m}	53 m}	
VMP (130)	80%}†	20%†	24% [b]	32 m}†	63 m*	GEM2005MAS65[44,199]
VTP (130)	81%	28%	20%	23 m	43 m	
VMPDara(346)	91%*	43%*	22%*c	72% at 18 m*		ALCYONE[85]
VMP(354)	74%	24%	6%	50% at 18 m		
VP (51)	64%	8%		14 m	60% at 2 years	Italy
VCP (51)	67%	2%		15 m	70% at 2 years	(Phase 2)[66]
VMP(50)	86%	14%		17 m	76% at 2 years	

Post-induction protocols varied, with consolidation and maintenance treatments given depending on trial protocol. Comparison of survival data between trials should be viewed with caution.

[a]Trial includes 69% with intention to transplant [b]1×10^{-4} [c]1×10^{-5}.

Comparison of survival data between trials should be viewed with caution.

*Significant difference, $P < 0{\cdot}05$.

†Not significant. Where not indicated, statistical differences were not reported.

Table X. Carfilzomib-based induction regimens.

	After Induction			After ASCT/Cons				
Regimen (*n*)	ORR (≥PR)	CR rate	MRD-	ORR (≥PR)	CR rate	MRD negative	PFS	Trial/Group name
KCRD (526)	90%	18%		98%	32%		64·5% at 3 years*	UK Myeloma XI [58,73]
CTD (265)	86%	7%		94%	25%		}50·3% at 3 years	
CRD (265)	90%	7%		97%	23%		}	
KRDautoKRD}(309)					49%}*	58%}*[a]		FORTE[69]
KRD12}					52%}	54%}		
KCDautoKCD (154)					38%	41%		
KRD (45)				98%		62%[b] (MRD- CR)		USA (Phase 2)[200]

[a]1×10^{-5}, [b]MRD- CR, 1×10^{-5}.

Post-ASCT protocols varied, with tandem auto, consolidation and maintenance treatments given depending on trial protocol. Comparison of survival data between trials should be viewed with caution.

*Significant difference, $P < 0{\cdot}05$.

In NTE populations, VCD and VMP are commonly used induction regimens, with the VISTA VMP schedule widely used, and showing a survival advantage over both MP[82] and VTP.[83] The UPFRONT study, however, showed equivalent benefit for VD alone compared to VMP or VTD, again reinforcing the importance of the PI/steroid backbone,[68] as was shown in a similar Phase 2 study of VP, VCP and VMP.[66]

Addition of Monoclonal Antibody

Daratumumab has been added to various induction regimens, demonstrating improved RR and PFS for NTE patients in combination with RD,[84] and both PFS and OS with VMP,[85,86] and PFS for TE patients in combination with VTD.[84,87] OS data remain immature, but PFS data provide early evidence of benefit, and it is likely to be rapidly adopted into the frontline setting.

Non-PI-based Regimens

Non-PI-based combinations are an option in frailer patients for whom an all oral regimen is preferred (Table XI). For patients without high-risk cytogenetic features, these may be more tolerable and therefore more beneficial for long-term use. In this

Table XI. NTE regimens Non-PI-based.

Regimen	ORR (≥PR)	CR rate	MRD-	PFS	OS	Trial/Group name
RDcont(535)	75%}*	15%		26 m*	59 m}*	FIRST[88,95]
RD18 (541)	73%}	14%		21 m}	62 m}	
MPT18(547)	62%	9%		22 m}	49 m	
MPT (318)	81%	10%		20 m†	52% at 4 years†	HOVON87/NMSG18[89]
MPR (319)	84%	13%		23 m	56% at 4 years	
MPT (154)	75%	5%		21 m†	53 m†	ECOG E1A06[93]
MPR (152)	70%	11%		19 m	48 m	
RD-Dara(368)	93%*	48%*	24%*[a]	71% at 30 m*		MAIA[84]
RD(369)	81%	25%	7%	56% at 30 m		

Post-induction protocols varied, with consolidation and maintenance treatments given depending on trial protocol. Comparison of survival data between trials should be viewed with caution.

[a]1×10^{-5} (ClonoSeq).

*Significant difference, $P < 0{\cdot}05$.

†Not significant. Where not marked, statistical differences were not reported.

context, RD has been shown to be more effective than MPT due to greater efficacy and better long-term tolerability.[88,89]

The addition of an alkylating agent to an IMiD/steroid combination (e.g., CTD, CRD) can deepen responses,[90,91] although survival benefits have not been demonstrated.

Lenalidomide-based combinations are generally preferred to thalidomide-based ones, with improved survival in CRD compared to CTD in TE patients,[92] and similar responses but better tolerability shown with MPR *versus* MPT in NTE patients.[93]

Duration of Induction Therapy and Timing of Transplant

For TE patients, treatment is continued to maximal response with minimal toxicity, generally between four and six cycles before harvest and ASCT. With lenalidomide-containing regimens, harvest should be performed after 4 cycles to prevent inadequate stem cell yield.

For NTE patients, there is a move to continuous therapies —for example, with lenalidomide and daratumumab. This is based on improved PFS in the Myeloma XI[94] and FIRST trials,[95] although there remains uncertainty as to the benefit in terms of overall survival. The VMP regimen is, however, for a fixed duration, as per the VISTA trial. The aim should be treatment delivery and tolerability, using reduced doses if necessary.

Salvage for Suboptimal Response

Patients achieving less than a PR may benefit from switching to an alternative schedule. The Myeloma XI trial data demonstrated that patients achieving less than a VGPR following CTD or CRD induction benefit from switching to a bortezomib-based regimen.[96] However, most patients will now receive bortezomib as initial therapy. Many units use DT-PACE (with or without bortezomib) or similar regimens in fit patients to achieve a deeper response prior to transplant, although there is a lack of data in this area.

Treatment of High-risk Disease

As above, high-risk myeloma is defined by a number of factors, of which cytogenetics have the main impact on initial treatment selection. There is evidence that PI-based therapy may abrogate the risk of t(4;14) and 17p−, and should therefore be used in these patients if possible.[80,97] In older NTE patients, this should prompt the use of a PI-based regimen (e.g., VMP) above an oral non-PI combination (e.g., RD) where tolerated. This approach is supported by a pooled analysis of two separate trials of VMP and RD.[98]

For patients presenting with cast nephropathy-induced acute kidney injury, plasma cell leukemia or with a proliferative phenotype, biweekly bortezomib with high dose blocks of dexamethasone can be used for initial treatment. Intensive cytotoxic-containing regimens such as (V)DT-PACE are occasionally used for rapid debulking and for more aggressive presentation in younger patients.

Recommendations

Treatment should be chosen according to individual patient factors to maximise the depth and duration of response while minimising toxicity, in order to lengthen survival, improve quality of life, alleviate symptoms and prevent further organ damage. (1A)

Treatment combinations should be selected for individual patients based on efficacy, tolerability, transplant-eligibility, frailty, comorbidities, patient preference and local familiarity, as well as national and local licencing and payment criteria. (1A)

Transplant-eligible (TE) patients should receive a PI (bortezomib or carfilzomib)/corticosteroid-based induction regimen. (1A)

Triplet regimens deepen response and are generally recommended for TE patients with the addition of an IMiD (e.g. VRD, VTD, KRD) preferred to cyclophosphamide (e.g., VCD, KCD). (1A)

For TE patients, the aim should be to achieve maximal response with typically four to six cycles of an induction regimen prior to consolidation with ASCT. Patients receiving a lenalidomide-containing induction regimen should receive a maximum four cycles prior to stem cell harvest. (1C)

Melphalan should be avoided in TE patient due to concerns about reduced yield at stem cell harvest. (1C)

For NTE patients, the aim should be to balance delivering tolerable treatment and minimising discontinuations whilst still using effective regimens. (1C)

NTE patients may receive a PI or non-PI-based treatment regimen. Patients with high-risk cytogenetics should receive a bortezomib/corticosteroid-based regimen if possible. For others, a lenalidomide-based, non-PI containing regimen is also acceptable, and may be preferred for patient-based factors. (1B)

For NTE patients, an alkylating agent (cyclophosphamide or melphalan) or IMiD (thalidomide or lenalidomide) agent may be added to a bortezomib/corticosteroid-based regimen. Lenalidomide is preferred to thalidomide. (2B)

Frailty assessment, including the use of objective scoring systems, should be carried out for older and less fit patients. A multidisciplinary approach with input from care of the elderly specialists may be beneficial. (1B)

Dose modifications should be considered for all frailer, less fit patients. (1A)

For patients achieving less than a PR, an alternative regimen may be considered in order to deepen response. (2C)

Daratumumab is well tolerated and improves response rates and survival. It can be added to combination regimens, as per licence. (2A)

Bortezomib should normally be given subcutaneously on a weekly regimen. (1A)

Patients with aggressive proliferative disease, plasma cell leukaemia or myeloma-induced cast nephropathy should receive biweekly bortezomib for initial treatment or, alternatively, a more aggressive combination schedule such as DT-PACE. (2C)

Autologous Stem Cell Transplantation

Autologous stem cell transplantation following high dose chemotherapy has been standard of care for consolidation following induction treatment in those considered fit enough, since it was first demonstrated to prolong PFS and OS with acceptable low levels of transplant-related mortality (TRM).[99] Subsequent randomised trials have shown improved response compared to chemotherapy alone.[100-104] A majority of these have also shown improved PFS, and although a significant OS advantage was not demonstrated in all trials, this is likely related to variation in induction and consolidation therapies, and the use of salvage ASCT in those not receiving it up front. On balance, therefore, ASCT has demonstrated its efficacy as post-induction consolidation (Table XII). More recently, given the increases in the rates and depths of remission achieved with the introduction of novel agents given in combination and the toxicities of high dose chemotherapy,

Table XII. Trials of ASCT.

Induction regimen (*n*)	ASCT conditioning	After ASCT/Cons					Trial/Group name
		ORR (≥PR)	CR rate	TRM	PFS	OS	
Pre-novel agent era							
VAMP + ASCT (201)	Mel200	82%	44%*	3%	32 m*	54 m*	UK MRC
ABCM + Cons (200)		48%	8%		20 m	42 m	Myeloma VII[100]
VMCP/BVAP + ASCT (100)	Mel140-TBI	81%*	22%*	3%	27 m*	NR at 41 m*	IFM[101]
VMCP/BVAP + Cons (100)		57%	5%		18 m	37 m	
VAMP + ASCT (91)	LEAM-TBI	86%	19%	10%	39 m	65 m*	MAG[102]
VMCP + Cons (delayed ASCT) (94)		62%	5%		13 m	64 m	
VAD + ASCT (261)	Mel140-TBI	76%†	11%†	3%	22 m†	48 m†	SWOG S9321[104]
VAD + VBMC Cons (255)		76%	11%		22 m	48 m	
VBMCP/VBAD + ASCT (81)	Mel140-TBI/		30%*	4%	42 m†	61 m†	PETHEMA[103]
VBMCP/VBAD + Cons (83)	Mel200		11%		33 m	66 m	
Novel agent era							
VRD + ASCT (350)	Mel200		59%*		50 m*	81% at 4 years†	IFM2009[105]
VRD + Cons (350)			48%		36 m	82% at 4 years	
VCD + ASCT (415)	Mel200/tandem				64% at 3 years*	85% at 3 years†	EMN02/HO95[145]
VCD + Cons (203)					57% at 3 years	85% at 3 years	

Where not indicated, statistical differences were not reported. Comparison of survival data between trials should be viewed with caution.
*Significant difference, $P < 0{\cdot}05$.
†Not significant.

its place in the upfront management of myeloma has been questioned.

Efficacy and Timing of ASCT

Two recent trials have attempted to address the role of ASCT following modern induction combinations and whether it could be reserved for a later line of therapy. The IFM2009 trial randomised 700 patients following VRD induction to ASCT or extended VRD consolidation. All patients received lenalidomide maintenance for 1 year. Median PFS (50 months vs. 36 months), CR rate and MRD negativity were all significantly longer in the ASCT group, maintained across all risk groups. There was, however, no OS benefit at 4 years (81% vs. 82%).[105]

In the EMN02/H095 trial,[106,107] a comparison of ASCT (single or tandem) with VMP consolidation after VCD induction, demonstrated upfront ASCT was associated with improved PFS (64% vs. 57% at 3 years) but again not OS (85% vs. 85% at 3 years).

These trials demonstrate that post-induction ASCT continues to deepen responses and prolong PFS in the novel agent era. The lack of OS benefit is likely to be largely due to the use of delayed ASCT in those who did not receive this up front. Although this supports the use of deferred ASCT as a clinical option, the fact that 21% of patients in the non-ASCT arm of the IFM2009 study were unable to receive ASCT at relapse due to disease refractoriness reinforces the benefit of upfront ASCT where feasible. Whether this paradigm remains true with the addition of a monoclonal antibody to a PI/IMiD induction regimen remains to be shown.

Location

ASCT should only be carried out in commissioned centres who have achieved JACIE accreditation. Where suitable facilities and policies are in place, the procedure can be done in an ambulatory setting.[108]

Stem Cell Mobilisation

Haematopoietic stem cells are usually harvested from the peripheral blood by apheresis, most commonly following mobilisation schedules of either cyclophosphamide (1·5–4 g/m^2) and granulocyte colony-stimulating factor (G-CSF) (5–10 μg/kg) ("Cyclo-G") or single-agent G-CSF (10 μg/kg).[109] The minimum CD34$^+$ stem cell dose considered sufficient for successful engraftment is 2×10^6 CD34$^+$ cells/kg.[110] Cyclo-G may result in higher yields, particularly in older patients, but results in increased rates of febrile neutropenia, especially with doses greater than 2 g/m^2.[111] Single-agent G-CSF is less toxic and easier to schedule for busy apheresis units.

For selected patients, collecting greater than 4×10^6 CD34$^+$ cells/kg to facilitate a potential second ASCT, either as part of second line treatment or for a planned tandem transplant, is appropriate.

For patients in whom there is failure to harvest sufficient stem cells, combining G-CSF and the chemokine CXCR4 receptor antagonist plerixafor (Uy 2008) can result in the successful achievement of target CD34+ numbers.[112] Reduced stem cell yields after prolonged induction treatment with lenalidomide are well described.[113] Cyclo-G mobilization has been reported to give better yields post-lenalidomide induction.[114] Lenalidomide upregulates CXCR4, increasing stem cell binding to bone marrow cells,[115] providing a rationale for the use of pre-emptive plerixafor in patients heavily pretreated with lenalidomide.[116]

In patients with severe renal failure, stem cells can be successfully mobilised using single-agent G-CSF.[117] Plerixafor can be used at a reduced dose in patients with a glomerular filtration rate (GFR) 20–50 ml/min, but there are no data to support its use in those with a GFR <20 ml/min.

Conditioning

The standard conditioning pre-ACST has been high dose melphalan (HDM), 200 mg/m^2, for many years.[110] Combination with other alkylating agents (e.g., busulphan,[118] total body irradiation,[119] multi-agent chemotherapy[120] and increased dose of melphalan)[121] have all been shown to increase toxicity.

A recent Phase 3 trial comparing intravenous busulfan and melphalan with HDM has shown improved PFS (Bu-Mel 65 m, HDM 43 m) but similar OS and higher toxicity.[122] Incorporation of bortezomib has shown no benefit.[123]

In the absence of convincing Phase 3 data, HDM remains standard of care.

Patient Selection Based On Age

The majority of the trial data for ASCT include patients <65 years; however, ASCT is feasible in those >65 years. Studies from the pre-novel agent era showed similar results in older patients to those of younger patients—improved response, but with variable results for PFS and OS, likely explained by similar factors as outlined above[124-126] (Table XIII).

Single-arm studies of bortezomib-based induction and ASCT in selected older patients show acceptable TRM and survival outcomes comparable to younger patients.[127,128] A *post hoc* analysis of UK Myeloma XI assessed outcomes in older patients receiving CTD/CRD induction and HDM ASCT. When compared to a matched cohort of older patients who did not receive a transplant, those undergoing ASCT had improved PFS and OS.[129]

These results support the ongoing trend for increased use of HDM ASCT in older patients.[130,131] Given that a cohort of nine octogenarian patients has been reported with a TRM of 0%,[132] there is no absolute upper age limit for high dose

Table XIII. Trials of ASCT in older patients.

Induction regimen	ASCT conditioning	After ASCT/Cons ORR (≥PR)	After ASCT/Cons CR rate	TRM	PFS	OS	Trial name/ Age range
Pre-novel agent era							
VAMP + ASCT(94)	Mel or Bu/Mel	83%	10%		25 m†	48 m†	France[124]
VMCP + Cons(96)		58%	4%		19 m	48 m	Age 55–65
VAD + ASCT(95)	Mel100	72%			37% at 3 years*	77% at 3 years*	Italy [125]
VAD + MPCons(99)		45%			16% at 3 years	61% at 3 years	Age 50–70
VAD + ASCT(126)	Mel100	65%}*	18%}*	9%	19 m	38 m	IFM 99-06[201]
MPx12 (196)		76%}	13%}		28 m*	52 m*	Age 65–75
MPTx12 (125)		35%	2%		18 m	33 m	
Novel agent era							
PAD (102)	Mel100	93%	33%	5%	48 m	63% at 5 years	Italy[127] 65–75 (Phase 2)
Bz-based (56)	Mel140/Mel200	94%	40%	0%	76% at 2 years	88% at 2yrs	Italy[128] 64–74 (Phase 2)

*Significant difference, $P < 0{\cdot}05$.

†Not significant. Where not indicated, statistical differences were not reported. Comparison of survival data between trials should be viewed with caution.

therapy as long as careful attention is paid to patient selection.

Consideration may be given to reducing the dose of melphalan to 100 or 140 mg/m^2 in those greater than 65 years.

Renal Impairment

The use of HDM and ASCT is feasible in patients with renal impairment, up to and including those requiring renal replacement therapy.[133,134] Careful selection of patients and close liaison with nephrology teams is essential. Patients with renal impairment are more likely to suffer from toxicity and have higher TRM, with up to 29% reported in historical series of those on dialysis at the time of transplant; however, outcomes are similar to those of matched controls.[135-137]

There are no randomised trials exploring the dose of melphalan in renal failure. 200 mg/m^2 is feasible,[137,138] but many centres reduce dose to 140 mg/m^2 for those with a GFR <30 ml/min and have reported better outcomes at lower doses.[139,140] A proportion of patients attain dialysis-independence after transplantation.[133,134,140]

Tandem ASCT

Tandem ASCT utilises a second transplant, with the same or modified conditioning within 3–6 months of the first, in patients without disease relapse or progression. A systematic review of six randomised controlled trials (RCTs) of more than 1,800 patients predating novel agents failed to demonstrate an improvement in OS or PFS in previously untreated patients.[141] However, subgroup analyses in two of the historical studies demonstrated an improved PFS and OS for those patients who did not reach at least a VGPR with the first transplant.[142,143]

Two more recent RCTs show differing results. The BMT-CTN0702 StaMINA trial demonstrated no benefit to tandem ASCT compared to single ASCT with RVD consolidation and lenalidomide maintenance.[144] In contrast, the EMN02/HO95 trial showed a PFS and OS benefit to tandem ASCT, and seemed to abrogate the effects of high-risk cytogenetic lesions.[145,146] A meta-analysis of three trials has also demonstrated PFS and OS advantage to tandem ASCT, particularly in patients with advanced ISS stage, adverse cytogenetics or failure to achieve CR.[147]

Recommendations

ASCT should be carried out in JACIE accredited facilities. (1C)

ASCT should be carried out at first remission after novel agent induction in those considered fit enough after full assessment. (1A)

Consideration can be given to delaying ASCT until after second or subsequent lines of therapy, if required by patient's circumstances or preference. (2B)

Mobilisation with Cyclo-G or G-CSF alone or with plerixafor is recommended, aiming for enough stem cells for two procedures if possible in those considered of an age to undergo a second procedure. (1A)

Conditioning with HDM at 200 mg/m^2 is the standard dose, with a dose reduction to 140 mg/m^2 recommended in those with GFR <30 ml/min or >65 years of age. (1B)

Tandem ASCT may be considered in those with poor risk clinical features, or who have not achieved a VGPR after the first transplant. (2A)

Patients with severe renal impairment or on renal replacement therapy may still be considered for ASCT with close liaison with nephrology teams. (2B)

Consolidation Therapy post-ASCT

Consolidation therapy involves the delivery of fixed duration of anti-myeloma treatment after ASCT. The objective of consolidation therapy is to achieve deeper responses and prolonged PFS and OS. Consolidation does appear to deepen response, but its impact on survival is less clear, with most benefit seen in cases where pre-ASCT treatment was limited. A number of studies have examined the use of bortezomib-based consolidation (Table XIV).

Bortezomib Monotherapy Consolidation

Single-agent bortezomib consolidation led to an improvement in RR and PFS, but not OS, in a trial of bortezomib-naive patients; the PFS benefit was primarily driven by patients not in VGPR post-ASCT.[148] A second study showed a PFS benefit for bortezomib monotherapy consolidation post-ASCT regardless of exposure to bortezomib induction. Again, greatest benefit was seen in patients achieving less than a VGPR post-ASCT, and in those with high-risk cytogenetics.[149]

VTD Consolidation

In a non-randomised study in patients who had received VAD (i.e., non-bortezomib) induction and achieved at least a VGPR post-ASCT, VTD consolidation deepened CR rates from 15% to 49% and improved major MRD response rates from 23% to 57%.[150] In a comparative study with TD, VTD induction and consolidation post-double ASCT deepened responses, with an increase in CR rate (61% vs. 49%) and 3-year PFS (60% vs. 48%). Patients who benefited most were those who did not achieve CR/near CR after double ASCT. Patients with high-risk cytogenetics (t(4;14) and/or 17p−) also appeared to benefit from VTD *versus* TD consolidation (3-year PFS 59% vs. 19%). However, no difference in OS was reported.[151]

VRD Consolidation

The incremental benefit of VRD consolidation is also primarily seen in response rate and PFS, but not OS. In contrast to the bortezomib-only and VTD trials reported above, most patients who received VRD consolidation had bortezomib-based induction regimens pre-ASCT. In a small Phase 2 non-randomised study of VRD induction and consolidation, there was a post-consolidation increase in CR/sCR rates from 47% to 50% and MRD negative CR from 54% to 58%.[63] The Phase 3 StaMINA study tested the impact of consolidation with ASCT + 4 × VRD consolidation *versus* tandem ASCT *versus* single ASCT, followed by 12 months' lenalidomide maintenance in all arms. Consolidation with VRD after induction and ASCT provided no PFS or OS advantage over maintenance alone, including in patients with high-risk cytogenetics (of note, 12% of patients were non-compliant with consolidation).[144] In this study, 73% of patients received triple-drug induction, VRD in 55% and VCD in 14%, suggesting that the benefits of bortezomib-based consolidation are less impressive in patients treated with effective bortezomib-based induction.

Table XIV. Post-ASCT consolidation therapy.

Transplant regimen (*n*)	Post-ASCT consolidation regimen (*n*)	PFS	OS	Trial/Group name
Bortezomib monotherapy				
Single ASCT (non-PI induction)	Bortezomib (187)	27 m*	80% at 3 years†	NMSG[148]
	Nil (183)	20 m	80% at 3 years	
Single/Tandem ASCT	Bortezomib (186)	34 m*	NS†	DSMM[149] MMY3012/3013
	Nil (185)	28 m		
VTD				
VTD + Tandem ASCT	VTD (160)	60% at 3 years*	90% at 3 years†	GIMEMA MMY-3006[151]
TD + Tandem ASCT	TD (161)	48% at 3 years	88% at 3 years	
VRD				
Single ASCT	Tandem ASCT + Len Maint (247)	59% at 38 m†	82% at 38 m†	BMT CTN Stamina[144]
	VRD Cons + Len Maint (254)	58% at 38 m	85% at 38 m	
	Len Maint (257)	54% at 38 m	84% at 38 m	
VCD + ASCT or VMP	VRD + Len Maint (455)	48% at 5 years*	87% at 3yrs†	EMN02/HO95[62,152]
	Nil + Len Maint (437)	41% at 5 years*	86% at 3yrs	

*Significant difference, $P < 0{\cdot}05$.

†Not significant. Where not indicated, statistical differences were not reported. Comparison of survival data between trials should be viewed with caution.

In the EMN02/HO95 trial, consolidation with VRD post-induction with VCD followed by 4 × VMP or HDM ASCT (single or double) demonstrated an advantage to consolidation in terms of PFS (5 year PFS 48% vs. 41%); both arms received lenalidomide maintenance. When adjusted for the first randomisation, there was a PFS benefit for consolidation which was retained across most predefined subgroups, including revised-ISS stage I and III, low-risk cytogenetics, in patients randomised to either VMP or HDM (HR = 0·84), but not in patients with high-risk cytogenetics [del(17p) and/or t(4;14) and/or t(14;16)].[152] Again, both groups did equally well in terms of OS (87% vs. 86% at 3 years).[62]

Non-bortezomib-based Consolidation Therapy

Data on carfilzomib and ixazomib-based consolidation strategies remain immature at the time of writing.

Maintenance Therapy post-ASCT

Maintenance therapy involves the ongoing delivery of anti-myeloma therapy until progression or toxicity. The goal of maintenance is to maintain a state of remission using a safe, non-toxic therapy (Table XV).

Thalidomide Maintenance

The earliest studies investigating the role of maintenance with thalidomide demonstrated a PFS advantage in patients without high-risk FISH. However, this did not translate into an OS advantage in most studies. Thalidomide is poorly tolerated, with significant grade 3–4 peripheral neuropathy rates of up to 19%, frequently leading to early discontinuation.[153-155]

Lenalidomide Maintenance

Four large randomised controlled studies (CALGB 100104,[156] GIMEMA,[157] IFM 2005-02[158] and UK MRC Myeloma XI)[94] have demonstrated a PFS advantage for lenalidomide, with two studies (CALGB 100104[156] and UK MRC Myeloma XI)[94] also showing an OS advantage (Table XIV). Of note, only the UK Myeloma XI study was powered to detect OS as a primary endpoint. Furthermore, meta-analyses prior and

Table XV. Post-ASCT maintenance therapy.

Transplant regimen (*n*)	Maintenance regimen (*n*)	PFS	OS	Trial/Group name
Thalidomide				
Tandem ASCT	Nil (200)	36% at 3 years}	77% at 4 years}	IFM[153]
	Pamidronate (196)	37% at 3 years}	74% at 4 years}	
	Pamidronate + Thal (201)	52% at 3 years*	87% at 4 years*	
Single/Tandem ASCT	IFN + Thalidomide (323)	56% at 5 years*	65% at 5 years†	UAMS[154]
	IFN (345)	44% at 5 years	65% at 5 years	
Single ASCT	Thalidomide (245)	30 m*	75% at 3 years†	UK MRC[155]
	Nil (247)	23 m	80% at 3 years	
Lenalidomide				
Single ASCT	Lenalidomide (231)	57 m*	114 m*	CALGB 100104[159]
	Placebo (229)	29 m	84 m	
ASCT or MPR	Lenalidomide (126)	42 m*	88% at 3 years†	GIMEMA RV-MM-PI-209[157]
	Nil (125)	22 m	79% at 3 years	
Single/Tandem ASCT	Lenalidomide (307)	41 m*	80% at 3 years†	IFM 2005-02[158]
	Placebo (307)	23 m	84% at 3 years	
Single ASCT	Lenalidomide (730)	57 m*	88% at 3 years*	MRC Myeloma XI[94]
	Placebo (518)	30 m	80% at 3 years	
Bortezomib				
PAD + Single/Tandem ASCT	Bortezomib (230)	34 m*	91 m†	HOVON-65/GMMG-HD4[81]
VAD + Single/Tandem ASCT	Thalidomide (270)	28 m	82 m	
Single ASCT	Bortezomib/Thalidomide (91)	51 m*	78% at 5 years†	GEM05/MENOS65[162]
	Thalidomide (88)	40 m}	72% at 5 years	
	Interferon (92)	33 m}	70% at 5 years	
Ixazomib				
Single ASCT	Ixazomib (395)	27 m*		TOURMALINE-MM3
	Placebo (261)	21 m		

*Significant difference, $P < 0·05$.

†Not significant. Where not indicated, statistical differences were not reported. Comparison of survival data between trials should be viewed with caution.

subsequent to the UK MRC Myeloma XI trial have demonstrated an OS benefit compared with placebo/observation (HR 0·75; 95% CI 0·63–0·90; $P = 0.001$) and (HR 0·72, 95% CI 0·56–0·91), respectively.[94,159]

Myeloma XI was the first study powered to assess the effect of lenalidomide according to pre-specified subgroups and found that there was a PFS advantage across all cytogenetic risk groups, including that defined by high-risk disease. However, maintenance therapy did not overcome the impact of high-risk disease on PFS.[94]

Maintenance lenalidomide is associated with manageable toxicity and is better tolerated than maintenance thalidomide. The commonest grade 3–4 adverse events include neutropenia (23–50%) and thrombocytopenia (4–15%). There is an increased risk of second primary malignancies (SPMs): 5·3–14% *versus* 3–5%, which is independent of ASCT.[88,94,156-158,160] Approximately one third of SPMs in Myeloma XI were low-risk, non-melanomatous skin cancers, and there was no increase in the risk of haematological malignancy.[161]

Bortezomib Maintenance

Bortezomib maintenance was compared to thalidomide in the HOVON-65/GMMG-HD4 trial, although the induction regimens also differed (PAD vs. VAD). The bortezomib-containing arm improved the CR rate by 12%, as well as PFS, but not OS. Patients with high-risk disease defined by 17p− by FISH or renal impairment demonstrated particular benefit. Bortezomib maintenance was better tolerated than thalidomide maintenance, with 11% stopping due to toxicity compared with 30% ($P < 0·001$).[80,81] The combination of bortezomib and thalidomide improved PFS, but not OS, compared to thalidomide alone (or alfa-2b interferon).[162] In view of toxicity and route of administration, long-term administration of bortezomib may be challenging, but may be considered in patients with high cytogenetic risk.

Ixazomib Maintenance

The second-generation proteasome inhibitor, ixazomib, has been investigated as maintenance therapy post-induction with PI +/− IMiD and ASCT. Its once weekly oral dosing and acceptable toxicity profile make this drug attractive for maintenance. In a Phase 3 placebo-controlled study, 656 patients achieving at least a PR post-induction and ASCT were randomised to 3:2 to receive ixazomib or placebo for up to 24 months. After a median of 31 months, median PFS was better (27 months vs. 21 months) and this was related to a deepening of response (12% vs. 7% conversion to MRD negativity). Although this study was not powered to detect a PFS difference in pre-specified subgroups, there was a PFS benefit for the ixazomib group in patients aged >60 years and ISS Stage III disease. In the high-risk cytogenetics group, the 24-month PFS was greater with ixazomib (46% vs. 24%); however, this did not reach statistical significance at 30 months. There were low rates of peripheral neuropathy PN and no excess of SPM in the ixazomib group; quality of life was preserved and there was a low discontinuation rate of 7%. OS data remains immature.[163]

Other Agents

Trial data for carfilzomib maintenance or daratumumab maintenance are not mature at the time of writing.

Recommendations

There is insufficient evidence to recommend consolidation with bortezomib monotherapy, VTD or VRD post-ASCT. (2B)

Maintenance therapy with thalidomide is not recommended post-ASCT. (1B)

Maintenance therapy with lenalidomide is recommended post-ASCT. (1A)

Maintenance therapy with bortezomib is not routinely recommended post-ACST, but can be considered in patients with high-risk cytogenetics. (2B)

Maintenance therapy with ixazomib is an option post-ASCT. (2B)

Allogeneic stem cell transplantation

The role of allogeneic stem cell transplantation in myeloma remains controversial, although a graft-versus-myeloma (GvM) effect is well recognised.[164]

Myeloablative Allogeneic Transplantation

Myeloablative (MA) allogeneic transplantation with a matched family donor (MFD) has a high TRM and morbidity, although this has improved with time.[165,166] Studies have reported TRM of 17–53%, despite the long-term PFS of 22–36% and OS 28–44%, with follow-up between 5 and 7 years (Table XVI). Patient fitness and disease status at time of transplantation and post-transplant impact outcomes.[167-169] Comparison of long-term outcomes *versus* that of autologous transplant failed to show significant difference over 10 years.[170] Given that reduced intensity conditioning (RIC) achieves lower TRM and better outcomes than MA transplants,[171] MA allografting should only be considered in exceptional circumstances.

Non-myeloablative Allogeneic Transplantation

The increased use of RIC allogeneic transplantation in myeloma was driven by the need to reduce TRM, and is feasible with reported TRM of 10–16%.[172-176] The presence of chronic Graft Versus Host Disease (GVHD) is associated with the achievement of CR and OS/PFS benefit, in particular with limited chronic GVHD.[167] One strategy to support

Table XVI. Allogeneic transplant studies using myeloablative conditioning.

Conditioning regimen (*n*)	CR rate post-Allograft	TRM	PFS	OS	Study type
Cy/TBI (39)	47%	32%	13% at 5 years	28% at 5 years	Retrospective[202]
Mel/TBI (78)	55%	35%	36% at 5 years	44% at 5 years	Retrospective[202]
Bu/Cy/TBI (15)	53%	17%	31% at 6 years	77% at 6 years	Prospective (Phase 2)[203]
Cy/TBI (±Idarubicin) (53)	19%	34%	18 m	25 m	Prospective (Phase 2)[186]
Mel/TBI (36)	17%	53%	22% at 7 years	39% at 7 years	Prospective (Phase 3)[104]
Mel/TBI (72)	38%	22%	31% at 10 years	40% at 10 years	Retrospective[170]

Cy, cyclophosphamide; TBI, total body irradiation; Me, melphalan; Bu, busulphan.

Table XVII. Allo-SCT in myeloma using NMA/RIC conditioning after first autologous SCT.

Allograft conditioning regimen/control (*n*)	CR rate post-Allograft/Control	TRM	PFS	OS	Trial/Group name
Flu/Bu/ATG Allo (65)	33%	11%	25 m†	35 m†	IFM 99-03/04[204]
Tandem Auto (219)			30 m	41 m	
Flu/Mel Allo (25)	40%*	16%†	NR†	NR†	PETHEMA/GEM[205]
Tandem Auto (85)	11%	5%	31 m	58 m	
TBI (200 cGy) Allo (80)	55%*	10%	35 m*	80 m*	Italian[206]
Tandem Auto (82)	26%	2%	29 m	54 m	
Flu/TBI (2 Gy)	51%*	12%*	22% at 8 years*	49% at 8 years*	EBMT-NMAM2000[177]
Tandem Auto	41%	3%	12%	36%	
Flu/Mel (126)		12%	35 m*		German (13p− cases only)[207]
Tandem Auto (?73)			22 m		
TBI (200 cGy) Allo (189)	50%*	11%*	43% at 3 years†	77%†	BMT CTN 0102[208]
Tandem Auto (436)	40%	4%	46% at 3 years	80%	
TBI (2 Gy) (122)		16%*	28% at 6 years†	55% at 6 years†	HOVON 50 (Donor
Tandem Auto (138)		3%	22% at 6 years	55% at 6 years	vs. no-donor)[209]

Flu, fludarabine; Bu, busulphan; ATG, Anti-thymocyte globulin; Mel, melphalan; TBI, total body irradiation.
*Significant difference, $P < 0{\cdot}05$.
†Not significant. Where not indicated, statistical differences were not reported. Comparison of survival data between trials should be viewed with caution.

the kinetics of developing a GVM effect whilst the disease remains under control is to perform sequential autologous-RIC allogeneic transplants ("auto-RIC-allo"). Several "biological" (donor vs. no-donor) studies have been reported with mixed results (Table XVI), but two studies report a significant difference in favour of auto-RIC-allo. It appears that long-term follow-up is required to assess the benefits of the tandem auto-RIC-allo approach (Table XVII).[177,178]

Allogeneic Transplantation for High-risk Disease

The impact of high-risk cytogenetic abnormalities on relapse after allogeneic transplantation is uncertain.[179,180] Data for upfront allografting in high-risk groups based on R-ISS is limited. For plasma cell leukaemia, an auto-RIC allo approach may improve OS compared to other treatment options,[181] but this remains controversial.[182]

Conditioning and T Cell Depletion

Extensive chronic GVHD can be associated with significant morbidity and mortality. Strategies to reduce GVHD include T cell depletion using alemtuzumab or anti-thymocyte globulin (ATG), but these may result in loss of a GVM effect.[173,183-186] At present, there is insufficient evidence to recommend one conditioning approach *versus* another.

Donor Source

Early retrospective studies in myeloma with matched unrelated donor (MUD) transplants initially showed a significantly higher TRM than with a matched family donor (MFD),[187,188] but more recent studies show equivalence.[168,189] Alternative donor sources such as haploidentical donors[190] and cord blood[191] have been investigated, but should only be considered in the context of clinical trials.

Syngeneic Transplants

Syngeneic transplants have shown additional survival over autologous transplant, without the higher toxicity associated with an allogeneic donor.[192,193] This approach should be used when possible.

Immune Effector Cell Therapy

The development of chimeric antigen receptor T cells (CAR-T) therapies, such as the anti-BCMA autologous CAR-T bb2121, have shown promising results in early trials.[194] This novel approach is the subject of intense investigation, but concerns remain regarding long-term survival, and at present it remains an investigational treatment.

Recommendations

Patients interested in pursuing an allogeneic transplant should be referred to a specialist centre so that they can gain an understanding of the risks and benefits of this procedure. (1B)

Allogeneic transplantation where possible should be carried out in the context of a clinical trial. (1B)

Allogeneic transplant procedures for patients with myeloma in first response should only be considered for selected groups (e.g., young patients with ultra-high-risk disease or primary plasma cell leukaemia) because of the risk of significant transplant-related morbidity and mortality, preferably in a clinical trial. (1B)

Reduced intensity conditioning (RIC) MFD or MUD allogeneic transplant is a clinical option for selected patients, preferably in the context of a clinical trial. If carried out, RIC transplantation should generally be performed in first response following an autograft (auto-RIC allo), in patients with responsive disease, VGPR or greater. (1B)

Myeloablative MFD or MUD allogeneic SCT should only be considered in a clinical trial or in exceptional circumstances due to high up-front risks. (1B)

Cord blood and haploidentical transplants should only be done as part of a clinical trial. (1B)

The role of T cell depletion is unclear, and patients need to be advised of the relative risks of GVHD and relapse. At present, there is insufficient evidence to recommend one conditioning approach *versus* another. (1C)

Syngeneic Transplants Are Recommended in Place of Autologous Transplant, Where A Donor Is Available. (1C)

Immune effector cell therapy such as anti-BCMA CAR-T can currently be accessed only through clinical trials. Their role in replacing allogeneic transplantation is currently unproven. (1C)

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Declaration of Interests

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs, which may be viewed on request.

Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force, and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.org/guidelines).

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