Outcomes of maintenance Treatment using lenalidomide or Bortezomib in Multiple Myeloma patients post Autologous Stem Cell Transplantation

Thesis

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List of Abbreviations

Abb.	Full term
AML	Acute myeloid leukemia
ASCT	Autologous stem cell transplant
Bort	Bortezomib
CALGB	Cancer and leukemia group B
CBC	Complete blood count
CR	Complete remission
CRAB	C = calcium (elevated), R = renal failure, A = anemia, B = bone lesions
CT	Computerized tomography
CyBorD	Bortezomib intravenously, cyclophosphamide and dexamethasone
EFS	Event free survival
EMD	Extra medullary disease
ESR	Erythrocyte sedimentation rate
FISH	Fluorescence in situ hybridization
FLC	Free light chain
GEP	Gene expression profile
GEP	Gene expression profile
HDC	High-dose chemotherapy
HMT	Histone methyltransferase
HU	Hounsfield units
IFN	Interferons
IMiDs	Immunomodulatory drugs
IMWG	International myeloma working group
KRD	Carfilzomib, lenalidomide, and dexamethasone
KRD	Carfilzomib, lenalidomide, and dexamethasone
LDH	Lactate dehydrogenase

List of Abbreviations Cont...

Abb.	Full term
Len	Lenalidomide
MDS	Myelodysplasia
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MRC	Myeloma research council
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
mSMART	Mayo Stratification for Myeloma and Risk-adapted Therapy
NGS	Next generation sequencing
OS	Overall survival
PCL	Plasma cell leukemia
PD	Pomalidomide plus low-dose dexamethasone
PET	Positron emission tomographye
PFS	Progession free survival
PFS	Progression- free survival
PIs	Proteasome inhibitors
RANKL	Receptor activator for nuclear factor κ B ligand
Rd	Lenalidomide plus dexamethasone
S-2M	Serum - 2-microglobulin
sCR	Stringent CR
SCT	Stem cell transplant
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMM	Smouldering multiple myeloma
SPMs	Second primary malignancies

List of Abbreviations Cont...

Abb.	Full term
SPSS	Statistical Program for Social Science
TD-PACE	Thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide
TRM	Treatment related majority
TTP	Median time to progression
VCD	Bortezomib, cyclophosphamide, and dexamethasone
VGPR	Very good partial response
VRD	bortezomib, lenalidomide, and dexamethasone
VTD	Bortezomib, thalidomide, and dexamethasone
WBC	White blood celss

INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. Myeloma is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years ***(Siegel et al., 2016)***.

However, statistics also reveal that death rates have been falling an average 0.8% each year over the period of 2004 through 2013 due to availability of newer and more effective treatment options. Symptoms of the disease are bony aches, polyuria, gastrointestinal disturbances, rapid progress dehydration and renal impairment ***(Siegel et al., 2016)***.

Most patients have serum M-protein with or without associated urinary M-protein. In the Mayo Clinic review of 1027 patients newly diagnosed with MM, 20% of patients had secretory urinary M-proteins; however, 3% of patients had neither serum nor urine M-protein, and therefore had no secretory myeloma ***(Kyle et al., 2003)***.

Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications. The three main translocations are the t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23). Several studies have confirmed that patients with t(4;14) and

t(14;16) have a poor prognosis, while t(11;14) is believed to impart no increased risk ***(Gertz et al., 2005)***.

Recommends additional tests that may be useful under some circumstances. These include whole body MRI or whole body PET/CT scan ***(Durie et al., 2002)***.

Treatment of MM has been rapidly evolving because of the introduction of new classes of drugs, such as immunomodulatory drugs (IMiDs) ***(Brenner et al., 2008; McCarthy et al., 2017).***

In addition, there is increasing understanding of the tumor biology, creating the rationale for new combinations of therapies and new drug development ***(Anderson, 2011).***

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and in selected patients, primary therapy is followed by high-dose chemotherapy with autologous stem cell support. The 3-drug regimens is preferred than the 2-drug regimens as it's based on improved response rates, depth of response, and rates of progression- free survival (PFS) and overall survival (OS) seen with 3-drug regimens in clinical trials. However, the panel notes that doublets could be used if a patient is elderly and/or frail and unable to tolerate a 3-drug regimen ***(Anderson, 2011).***

The results have shown that primary therapy with bortezomib/ lenalidomide/dexamethasone is active and well

tolerated in all newly diagnosed patients with MM, transplant eligible as well as transplant ineligible ***(Richardson et al., 2010)***.

Autologous SCT results in high response rates and remains the standard of care after primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous SCT is associated with statistically significant higher response rates and increased OS and EFS when compared with the response of similar patients treated with conventional therapy ***(Attal et al., 1996)***.

The response rates were evaluated after induction therapy and after autologous SCT. Taking into consideration patients who actually underwent the autologous SCT, the CR rates were increased from 35% pre-transplant to 57% post-transplant, in the group treated with bortezomib, thalidomide, and dexamethasone as induction therapy and from 14% to 40% in the group treated with thalidomide and dexamethasone as induction therapy ***(Rosiñol et al., 2012)***.

Maintenance therapy with lenalidomide was found to significantly reduce risk of disease progression or death after both single and tandem transplantation compared with no maintenance. Bortezomib as Maintenance Therapy after Autologous SCT, the results from the HOVON study show that maintenance with single- agent bortezomib after autologous SCT is well tolerated and is associated with improvement of ORR ***(McCarthy et al., 2017)***.