Remission Possible: The Evolving Role of Post-Transplant Maintenance Therapy

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Disclosures

- I am a member of a Speaker's Bureau for Jazz Pharmaceuticals

Objectives

- Discuss the rationale for use of maintenance therapy following hematopoietic stem cell transplantation (HCT)
- Summarize maintenance therapy strategies utilized following autologous HCT (MM, lymphoma)
- Summarize maintenance therapy strategies utilized following allogeneic HCT (AML HMAs/TKIs, ALL TKIs)
- Identify appropriate candidates for post-transplant maintenance therapy

The Need for Maintenance Therapy

- Maintenance therapy following HCT is generally given for two different reasons:
  - Maintaining depth of response achieved using HCT in incurable disease states
  - Prevention of relapse in aggressive disease states or in patients with early detection of minimal residual disease (MRD) post-HCT
    - May be indefinite in duration or for a pre-defined period of time

Blood. 2016;128(6):763-73.

Ideal Properties of Maintenance Therapy Agents

- Easy to administer
  - Oral medications
  - Ability for administration via home infusion
- Able to maintain disease response with minimal toxicity
  - Ability to tolerate long-term
  - Infrequent need for follow-up
  - Do not interfere with graft-versus-leukemia effect or increase graft-versus-host disease (allogeneic HCT)
- Low financial burden

Blood Cancer J. 2017;7(e545):doi:10.1038/bcj.2017.23.

Maintenance Therapy Post-Autologous HCT:

Multiple Myeloma (MM)

NCCN Maintenance Recommendations

- Historical (v3.2016)
  - Preferred
    - Thalidomide (category 1)
  - Other
    - Bortezomib with prednisone or thalidomide (category 2B)
    - Interferon (category 2B)
    - Dexamethasone or prednisone (category 2B)
    - Thalidomide with prednisone (category 2B)
- Current (v3.2017)
  - Preferred
    - Lenalidomide (category 1)
  - Other
    - Bortezomib (category 2A)

NCCN Guidelines. Multiple Myeloma. v3.2017 . Accessed August 23, 2017.

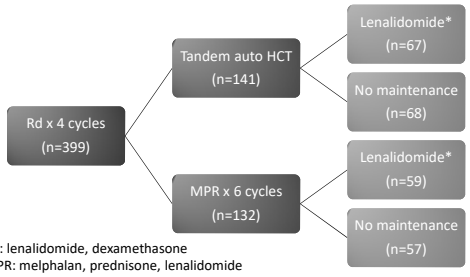
Lenalidomide Maintenance - Key Trials

	IFM 2005-02 (2012)	CALGB 100104 (2012)	Gay *et al*. (2015)
Population	n=614 Age <65 yrs SD or better after HCT	n=460 Age <71 yrs SD or better after HCT	n=389 Age <65 yrs Newly diagnosed MM
Start of Maintenance	After 2 months of lenalidomide consolidation	100 days post-auto HCT	3 months post-auto HCT
Treatment	Lenalidomide 10 mg daily x 3 months then ↑ to 15 mg daily until relapse vs. placebo	Lenalidomide 5-15 mg daily vs. placebo	Lenalidomide 10 mg + pred 50 mg daily (LP) days 1-21 vs. lenalidomide (L) alone
PFS/OS	PFS: 41 vs. 23 mos (p<0.0001) 4-yr OS: 70%	PFS: 46 vs. 27 mos (p<0.001) OS: 88% vs. 80% (p=0.03)	PFS: 37.5 mos (LP) vs. 28.5 mos (L) (p=0.34)
Adverse Effects	Secondary malignancies: 3.1 vs. 1.2/100 patient years (p<0.002)	Secondary malignancies: 7.8% vs. 2.6%	No difference

SD: stable disease; PFS: progression-free survival; OS: overall survival

Blood Cancer J. 2017;7(e545):doi:10.1038/bcj.2017.23.

Lenalidomide Maintenance – GIMEMA Trial



Rd: lenalidomide, dexamethasone
MPR: melphalan, prednisone, lenalidomide

*Dose: 10 mg daily days 1-21 of every 28 day cycle

N Engl J Med. 2014;371:895-905.

Lenalidomide Maintenance – GIMEMA Trial

- Median progression-free survival
  - Lenalidomide maintenance: 41.9 months
  - No maintenance: 21.6 months
  - p<0.001
  - No difference in PFS between auto SCT and MPR groups
- 3-year overall survival (%)
  - Lenalidomide maintenance: 88%
  - No maintenance: 79.2%
  - Not statistically significant

N Engl J Med. 2014;371:895-905.

Lenalidomide Maintenance – GIMEMA Trial

Grade 3-4 Adverse Events (%)	Lenalidomide Maintenance	No Maintenance	P-value
Neutropenia	23.3	0	<0.001
Infection	6	1.7	NS
Dermatologic	4.3	0	0.03
Venous thromboembolism	1.7	0	NS
Secondary malignancies	4.3	4.3	NS

- 14.7% of lenalidomide patients required dose reductions due to adverse events
- 5.2% of lenalidomide patients discontinued therapy due to adverse effects

N Engl J Med. 2014;371:895-905.

Secondary Malignancies with Lenalidomide

- Meta-analysis of all randomized, phase III trials in newly diagnosed multiple myeloma where at least one study group received lenalidomide
  - 7 trials included, n=3,254
  - 80.5% of patients received lenalidomide
    - Post-auto HCT: 30% received lenalidomide vs. 38% did not
- 5-year incidence of all cancers: 6.9% vs. 4.8% (p=0.037)
  - Hematologic: 3.1% vs. 1.4% (p=0.029)
  - Solid: 3.8% vs. 3.4% (p=0.72)
  - 1 death in each group due to secondary malignancy
  - Higher incidence in combination with PO melphalan (p<0.0001) but no difference with cyclophosphamide

Lancet Oncol. 2014;15:333-42.

Bortezomib Maintenance

	HOVON-65/GMMG-HD4 (2012)	PETHEMA-GEM (2012)
Population	n=827 Age <65 yrs	n=386 Age <65 yrs SD or better after HCT
Start of Maintenance	4 weeks post-auto HCT	3 months post-auto HCT
Treatment	Bortezomib 1.3 mg/m^2 q2 weeks vs. thalidomide 50 mg daily x 2 yrs	Thalidomide+bortezomib (TV) vs. IFN vs. thalidomide (T) x 3 yrs
PFS/OS	PFS: 35 vs. 28 mos (p=0.002) 5-yr OS: 61% vs. 55% (p=0.11) 5-yr PFS (del 17p): 22% vs. 5% 5-yr OS (del 17p): 65% vs. 18%	2-yr PFS: 78% vs. 63% vs. 49% (p=0.01) OS: No difference Increase in CR rate from 53 to 74% (TV) vs. 60% (T) (p=0.04)
Adverse Effects	30% discontinued treatment due to toxicity with thalidomide vs. 11% with bortezomib (p<0.001)	Increased thrombocytopenia (p=0.01) and peripheral neuropathy (NS) with TV vs. T

SD: stable disease IFN: interferon; PFS: progression-free survival; OS: overall survival

Blood Cancer J. 2017;7(e545):doi:10.1038/bcj.2017.23.

Ongoing MM Post-HCT Maintenance Trials

- Ixazomib
  - Phase I-III, single agent and in combination with lenalidomide
- Carfilzomib
  - Phase II-III, single agent and in combination with lenalidomide+dexamethasone
- Elotuzumab
  - Phase I-III, single agent and in combination with lenalidomide +/- bortezomib
- Daratumumab
  - Phase I, single agent
- Vorinostat
  - Phase I-III, in combination with lenalidomide or bortezomib
- Panobinostat
  - Phase I-II, single agent and in combination with lenalidomide

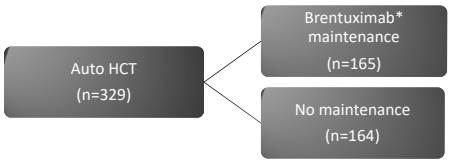
Blood Cancer J. 2017;7(e545):doi:10.1038/bcj.2017.23.
https://clinicaltrials.gov/. Accessed August 20, 2017.

Maintenance Therapy Post-Autologous HCT:

Lymphoma

Post-HCT Maintenance Brentuximab in Hodgkin Lymphoma (HL)

- AETHERA trial: Phase III multicenter, randomized double-blind, placebo-controlled trial of unfavorable-risk relapsed or refractory HL patients

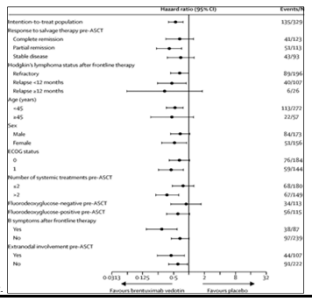


*Dose: 1.8 mg/kg q3 weeks for 16 cycles, starting 30-45 days post-HCT

Lancet. 2015;385(9980):1853-62.

Post-HCT Maintenance Brentuximab in HL AETHERA Trial

- 2-year PFS: 65% vs. 45% (p=0.0013)



Lancet. 2015;385(9980):1853-62.

Post-HCT Maintenance Brentuximab in HL AETHERA Trial

- Dose reductions due to adverse events required in 32% of brentuximab vs. 3% of placebo patients
  - Lead to delay in dosing in 9% of doses for brentuximab vs. 3% for placebo
- Most common adverse event in brentuximab group was peripheral neuropathy
  - Lead to discontinuation in 23% of patients
- Neutropenia and infections were other common adverse effects occurring more frequently with brentuximab
  - 25% of brentuximab patients required growth factor support vs. 11% of placebo patients

Lancet. 2015;385(9980):1853-62.

Post-HCT Maintenance Brentuximab in HL

- NCCN recommends maintenance brentuximab following autologous HCT in the following scenarios (category 2A):
  - Consider for Deauville 1-3 patients
  - Strongly consider for Deauville 4 patients
  - Only recommended for 1 year post-HCT
- Also states that the value of post-HCT maintenance brentuximab is unclear if patient received brentuximab pre-HCT as no OS benefit has been documented in the literature

NCCN Guidelines. Hodgkin Lymphoma. v1.2017 . Accessed August 23, 2017.

Post-HCT Maintenance Rituximab in Mantle Cell Lymphoma (MCL)

- Single-center retrospective review of 157 MCL patients who underwent autologous HCT
  - 50 went on to receive maintenance rituximab
    - 375 mg/m^2 dose given according to a variety of dosing schedules
    - Initiated at a median of 77 days post-HCT
    - Median of 8 doses received
  - 107 went on to receive observation alone

Ann Oncol. 2015;26(11):2323-28.

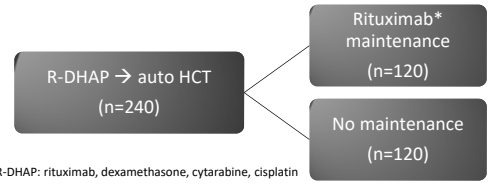
Post-HCT Maintenance Rituximab in Mantle Cell Lymphoma (MCL)

- Results at median follow-up of 5 years
  - PFS: HR 0.44 (95% CI: 0.24-0.8, p=0.007)
  - OS: HR 0.46 (95% CI: 0.23-0.93, p=0.03)
    - Benefit retained after multivariate analysis
  - Adverse events
    - Increased rate of grade 4 neutropenia with maintenance rituximab (34% vs. 18%, p=0.04)
    - No increase in non-relapse mortality observed with use of rituximab maintenance

Ann Oncol. 2015;26(11):2323-28.

Post-HCT Maintenance Rituximab in MCL – LyMA Trial

- Phase III international randomized trial of young (age <66 yrs), previously untreated >stage 1 MCL patients



R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin

*Dose: 375 mg/m^2 q8 weeks x 3 years

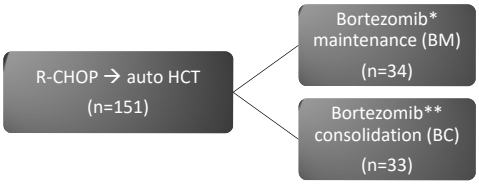
Hematol Oncol. 2017;35(S2):doi: 10.1002/hon.2438_74.

Post-HCT Maintenance Rituximab in MCL – LyMA Trial

- Results
  - 4-year PFS: 82.2% vs. 64.6% (p=0.0005)
  - 4-year OS: 88.7% 81.4% (p=0.0413)
  - 60% reduced risk of progression and 50% reduced risk of death with maintenance rituximab (p=0.0007, p=0.0454)
- Maintenance rituximab is now an NCCN category 1 recommendation following autologous HCT in patients with aggressive stage II (bulky) - stage IV disease

Hematol Oncol. 2017;35(S2):doi: 10.1002/hon.2438_74.

Post-HCT Maintenance Bortezomib in MCL CALGB 50403



R-CHOP: rituximab, cyclophosphamide, vincristine, prednisone

*Dose: 1.6 mg/m^2 weekly 4/8 weeks x 18 months, starting 90 days post-HCT
**Dose: 1.3 mg/m^2 days 1,4,8,11 of a 3 week cycle x 4 cycles, starting 90 days post-HCT

Blood. 2015;126:337.

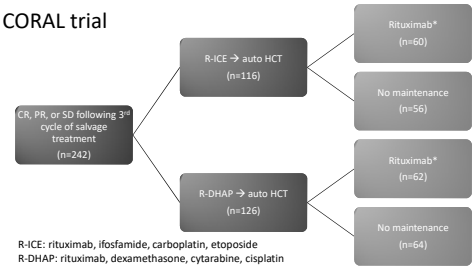
Post-HCT Maintenance Bortezomib in MCL CALGB 50403

- Results
  - 5-year PFS: 70% (BM) vs. 69% (BC) compared to null ($p<0.001$)
- Treatment discontinuation due to adverse effects
  - 13% (BM) vs. 28% (BC)
  - Most common adverse events were cytopenias and peripheral neuropathy

Blood. 2015;126:337.

Post-HCT Maintenance Rituximab in Diffuse Large B-Cell Lymphoma (DLBCL)

- CORAL trial



R-ICE: rituximab, ifosfamide, carboplatin, etoposide
R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin

*Dose: 375 mg/m^2 q8 weeks x 1 year, starting 28 days post-HCT

CR: complete response; PR: partial response; SD: stable disease

J Clin Oncol. 2012;30(36):4462-69.

CORAL Trial Results

4-Year Progression-Free Survival (%)

Patient Group	Rituximab Maintenance	No Maintenance	P-value
All patients (n=242)	52	56	0.8
R-ICE (n=116)	50	49	0.5
R-DHAP (n=126)	55	63	0.4

4-Year Event-Free Survival (%)

Patient Group	Rituximab Maintenance	No Maintenance	P-value
All patients (n=242)	52	53	0.7
R-ICE (n=116)	50	47	0.4
R-DHAP (n=126)	55	59	0.7

J Clin Oncol. 2012;30(36):4462-69.

CORAL Trial Results

- Adverse effects
  - Infection and neutropenia were most common
  - Pre-day 100 post-HCT:
    - 47% (rituximab) vs. 42% (no maintenance)
  - Post-day 100 post-HCT:
    - 30% (rituximab) vs. 17% (no maintenance)
- Death
  - Rituximab maintenance: 6
    - 2 secondary malignancies, 4 infections
  - No maintenance: 3
    - 2 secondary malignancies, 1 infection

J Clin Oncol. 2012;30(36):4462-69.

Ongoing Lymphoma Post-HCT Maintenance Trials

- Romidepsin (T-cell lymphoma - post-allo HCT)
  - Phase II
- Brentuximab (HL - post-allo HCT)
  - Terminated (slow accrual)
- Bortezomib
  - Phase II, single agent (MCL) and in combination with vorinostat (DLBCL, HL, MCL, T-cell lymphoma, follicular lymphoma)
- Lenalidomide
  - Phase III (MCL), phase I (HL)
- Ixazomib (MCL)
  - Phase I/II
- Panobinostat (HL)
  - Phase III
- Idelalisib (DLBCL, MCL, follicular lymphoma - post-allo HCT)
  - Phase I
- Ibrutinib (DLBCL)
- Pidilizumab (DLBCL)
- Nivolumab (HL)

https://clinicaltrials.gov/. Accessed August 20, 2017.

Maintenance Therapy Post-Allogeneic HCT:

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS)

Hypomethylating Agents - Key Trials

	Oshikawa *et al*. (2014)	Antar *et al*. (2014)
Population	n=10 AML	n=9 MDS, AML
Start of Maintenance	Median of 79 days post-HCT	Median of 100 days post-HCT
Treatment	Azacitidine 30 mg/m^2 x 7 days q4 weeks x 4 cycles	Azacitidine 32 mg/m^2 x 5 days q4 weeks x 12 cycles
PFS/RFS/OS	1-yr RFS: 60% 1-yr OS: 70%	1-yr PFS: 65% 1-yr OS: 90%
Adverse Effects	Infection and myelosuppression	Mild thrombocytopenia in 2 patients
GVHD	50% incidence of chronic GVHD	No GVHD exacerbations

PFS: progression-free survival; OS: overall survival; RFS: relapse-free survival; GVHD: graft-versus-host disease

Blood. 2016;128:763-73.

Hypomethylating Agents - Key Trials

	Pusic *et al*. (2015)	Gill *et al*. (2015)
Population	n=22 AML	n=34 MDS, AML
Start of Maintenance	50-100 days post-HCT	
Treatment	Decitabine 5-15 mg/m^2 x 5 days q6 weeks x 8 cycles	Azacitidine 100 mg/m^2 x 3 days q4 weeks x 8 cycles (or progression)
RFS/OS	2-yr RFS: 48% 2-yr OS: 56%	2-yr PFS: 66.1% (1st), 25% (2nd) 2-yr OS: 73.2% (1st), 14% (2nd) Full donor chimerism achieved in all patients
GVHD	41% aGVHD; 63% cGVHD	31.8% aGVHD; 77% cGVHD (1st) 8.3% aGVHD; 41.7% cGVHD (2nd)

PFS: progression-free survival; OS: overall survival; RFS: relapse-free survival; a/cGVHD: acute/chronic graft-versus-host disease

Blood. 2016;128:763-73.

FLT3 Tyrosine Kinase Inhibitors – Key Trials

	Chen *et al*. (2014)	Pratz *et al*. (2015)
Population	Phase I dose-escalation trial n=22 FLT3-ITD AML	n=28 FLT3-ITD AML
Start of Maintenance	45-120 days post-HCT	30-120 days post-HCT
Treatment	Sorafenib 200-400 mg BID x 1 yr	Sorafenib 200 mg QOD-400 mg BID for median of 252 days post-HCT
PFS/OS	1-yr PFS: 85% 1-yr OS: 95%	6 deaths (3 relapse), 5 relapses
Adverse Effects	5 patients discontinued due to toxicity (weight loss, GI symptoms)	Not reported
GVHD	38% incidence	32% incidence of ≥grade II

PFS: progression-free survival; OS: overall survival; GVHD: graft-versus-host disease

Blood. 2016;128:763-73.

Midostaurin Maintenance

- Prospective, phase II trial in newly diagnosed *FLT3*-ITD AML receiving midostaurin maintenance therapy post-allogeneic HCT
  - 50 mg daily for 1 year post-HCT (n=40)
- Results
  - Cumulative incidence of relapse: 12% (*FLT3* mutant:wildtype ratio <0.5), 5% (*FLT3* mutant:wildtype ratio ≥0.5)
  - Low incidence of adverse events (four grade 3-4 events)

Blood. 2015;126:322.

Lenalidomide Maintenance – LENAMAINT Trial

- Prospective, single center, phase II trial in high-risk AML/MDS patients with del5q (n=10)
- Lenalidomide maintenance (10 mg daily days 1-21 q28 days) starting at a median of 2.5 months post-HCT for 12 cycles
- Trial stopped early due to increased incidence of acute graft-versus-host disease (GVHD)
  - 60% of patients developed grade III-IV GVHD within first 2 cycles of maintenance
  - GVHD resolved in 67% patients after lenalidomide discontinuation and steroid initiation

Hematologica. 2012;97(9):e34-5.

Panobinostat Maintenance – Panobest Trial

- Phase I/II dose-escalation study in high-risk MDS/AML
  - N=42 (37 AML, 5 MDS)
- Panobinostat initiated between day 60-150 post-HCT and continued for up to 1 year
- Schedule A dosing:
  - 10 mg thrice weekly (TIW) escalated to 30 mg TIW
- Schedule B dosing:
  - 20 mg thrice weekly (TIW) escalated to 40 mg TIW

Blood. 2015;126:4344.

Panobinostat Maintenance – Panobest Trial

- Results
  - Recommended phase II dosing:
    - 20 mg TIW weekly or 30 mg TIW every other week
  - 2-year OS: 88%
  - 2-year disease-free survival (DFS): 74%
  - 19 patients discontinued therapy early
    - 10 due to adverse effects, 6 due to relapse, 3 for other reasons
    - Most common adverse effects were hematologic and GI toxicity
  - Cumulative incidence of moderate or severe chronic GVHD was 24% at 1-year post-HCT

Blood. 2015;126:4344.

Conclusions Regarding Post-HCT Maintenance in AML

- Maintenance therapy post-allogeneic HCT is currently not recommended by any guidelines, including NCCN
- Very few published randomized trials assessing efficacy of maintenance therapy though results of available studies are promising
- Encourage patient participation in a maintenance therapy clinical trial

Ongoing AML/MDS Post-HCT Maintenance Trials

- Azacitidine
  - Phase II
- Decitabine
  - Phase II
- Sorafenib
  - Phase II
- Midostaurin
  - Phase II
- Quizartinib
  - Phase I
- Crenolanib
  - Phase II
- Panobinostat
  - Phase I/II

https://clinicaltrials.gov/. Accessed August 20, 2017.

Maintenance Therapy Post-Allogeneic HCT: **Acute Lymphoblastic Leukemia (ALL)**

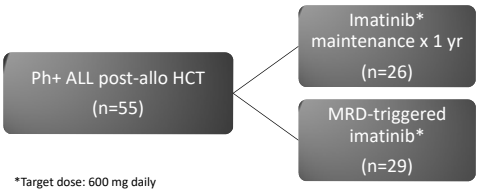
BCR-ABL Tyrosine Kinase Inhibitors – Key Trials

	CSTIBES02 (2010)	Chen *et al*. (2012)
Population	n=13 Ph+ ALL (4 auto HCTs)	n=62 Ph+ ALL
Start of Maintenance	Engraftment	Engraftment
Treatment	Imatinib 400 mg daily for a median of 9 mos post-HCT	Imatinib 400 mg daily for median of 3 mos
Outcomes	Relapse rate: 33% 4-yr OS: 30%	5-yr relapse rate: 10.2% vs. 33.1% (p=0.016) 5-yr DFS: 81.5% vs. 33.5% (p<0.0001)
Adverse Effects	20% discontinued treatment (GVHD, hematologic and GI toxicity)	16% discontinued treatment (hematologic and GI toxicity)

Ph+: Philadelphia chromosome-positive; DFS: disease-free survival; OS: overall survival; GVHD: graft-versus-host-disease

Cancer. 2016;122(19):2941-51.

BCR-ABL Tyrosine Kinase Inhibitors – Pfeifer *et al*. (2013)



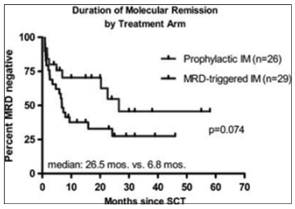
*Target dose: 600 mg daily

Ph+: Philadelphia chromosome-positive; MRD: minimal residual disease

Leukemia. 2013;271254-62.

BCR-ABL Tyrosine Kinase Inhibitors – Pfeifer *et al*. (2013)

- Results
  - Incidence of molecular recurrence
    - 40% vs. 69% (p=0.046)
  - 5-year OS:
    - 80% vs. 74.5% (NS)
  - Imatinib was discontinued in 67% of patients
    - GI intolerance was most common reason for discontinuation
    - GVHD incidence was not different between groups



Leukemia. 2013;271254-62.

Recommendations Regarding Post-HCT Maintenance Tyrosine Kinase Inhibitors in ALL

- NCCN:
  - Tyrosine kinase inhibitor (TKI) maintenance following allogeneic HCT in patients Philadelphia chromosome-positive (Ph+) ALL is a category 2A recommendation
  - Therapy should be initiated within 90 days post-HCT and continue for 1 year post-HCT
- European Society for Blood and Marrow Transplantation:
  - All Ph+ ALL patients are candidates for post-HCT TKI therapy to reduce relapse risk
  - A prophylactic (maintenance) or preemptive strategy can be used
  - Imatinib is first-choice TKI unless resistance is documented
  - Dasatinib is first-choice TKI in patients with a history of central nervous system involvement
  - Should be given for 12 months of continuous MRD negativity (if HCT in CR1) or indefinitely until unacceptable toxicity(if HCT in CR2)

NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2017 . Accessed August 23, 2017.
Cancer. 2016;122(19):2941-51.

Ongoing AML/MDS Post-HCT Maintenance Trials

- Blinatumomab
  - Phase II
- Lenalidomide
  - Phase I

https://clinicaltrials.gov/. Accessed August 20, 2017.

Summary

- Disease states with documented evidence supporting post-autologous HCT maintenance therapy include:
  - Multiple myeloma, Hodgkin lymphoma, mantle cell lymphoma
- Disease states with documented evidence supporting post-allogeneic HCT maintenance therapy include:
  - Acute myeloid leukemia/myelodysplastic syndromes, Philadelphia chromosome acute lymphoblastic leukemia
- Patients must be carefully selected and risks vs. benefits of further treatment must be assessed prior to initiation of maintenance therapy

Remission Possible: The Evolving Role of Post-Transplant Maintenance Therapy

Questions?

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