Association of Northern California Oncologists
Hematologic Malignancies Updates: Leukemias, Lymphomas, and Myeloma

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Panel Members

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Case 1

- 44 yo woman with no significant PMH presents to the ED with 1 month of fatigue, indigestion and progressive DOE; while in the ED patient complained of 15 minutes of blurry vision in her L eye
- Exam was unremarkable with no bruising, splenomegaly or lymphadenopathy; visual field without deficit upon examination
- Labs were remarkable for the following:

Lab	Value
WBC	145 K/mm^3
Hgb	8 g/dL
Plt	77K/mm^3
Blasts	54%
ANC	16 K/mm^3

Lab	Value
Potassium	3.4 mmol/L
Creatinine	0.61 mg/dL
LDH	1700 U/L
Uric Acid	3.4 mg/dL
D-Dimer	900 ng/mL

- Patient undergoes leukapheresis and is started on Hydroxyurea
- BMBx is completed and aspirate review reveals a markedly hypercellular marrow (90%) diffusely involved with myeloblasts (70%)
  - Flow cytometry confirms blasts express myeloid markers; CD33 is positive
  - Diagnosis of AML is confirmed
- TTE shows a normal EF

Case 1

- What regimen should be considered for this patient (ECOG = 0) based on the available information?

A. 7+3

B. 7+3 + Gemtuzumab ozogamicin

C. None, await molecular studies and cytogenetics

D. Daunorubicin and Cytarabine liposome

E. 7+3 + Midostaurin

Case 1

What benefit is gained from the addition of Midostaurin in FLT3 mutated AML?

A. Improved Overall Survival and Event Free Survival

B. Decreased need for allogeneic HCT in CR1

C. Less toxicity

D. Improved CR rate

E. Decreased blast count

Case 1

- Her course was generally uncomplicated barring neutropenic fever and mucositis
- Next Generation Sequencing Myeloid Panel returned revealing only FLT3-ITD and NRAS mutations
- Day 21 BMBx was completed and revealed a cellular marrow (25%) with increased blasts (35%)
  - Cytogenetics 46 XX

Case 1

What regimen should be chosen for re-induction?

A. 7+3 + Midostaurin
B. Clinical Trial
C. FLAG-IDA
D. 7+3
E. MEC

Case 1

- She is re-induced with 7+3 + Midostaurin, again with her course being largely uncomplicated
- BMT was consulted and began workup for potential transplant
- BMBx on Day 60 showed a cellular marrow (20%) with increased blasts (15%), counts were not recovered
  - Cytogenetics 46 XX
  - FLT3-ITD Not Detected
  - Multiparameter Flow Cytometry for MRD revealed a population of abnormal myeloblasts (6%)

Case 1

Considering her persistent disease, what is the next best step?

A. Allogeneic HCT
B. 3rd induction with standard chemotherapy regimen (FLAG, MEC, etc.)
C. Clinical Trial
D. Enasidenib
E. Azacitadine/Venetoclax

Case 1

- She was enrolled on a Clinical Trial and was able to achieve a Morphological Leukemia Free State after 3 cycles of therapy
  - Multiparameter flow cytometry is positive for MRD with 4.9% abnormal blasts found
- In the interim, her brother was found to be a 10/10 HLA match donor
- Her course has otherwise been largely uncomplicated

Case 1

What does the presence of MRD indicate in AML?

A. Higher relapse rate

B. Increased need for HCT

C. Worse Survival

D. All of the above

Case 1

What is the role of allogenic transplant at this time?

A. No role, await count recovery and confirm CR

B. Proceed with matched related donor allogeneic HCT now without count recovery

C. Proceed with matched related donor allogeneic HCT after count recovery

D. No role, continue with Clinical Trial

E. Change chemotherapy regimens

Case 1

- Patient underwent matched related donor allogeneic HCT

Case 1

Is there a role for post-transplant FLT3-directed therapy as maintenance?

A. Yes, restart Midostaurin

B. No

C. Yes, start Sorafenib

D. Yes, if on a trial

Case 1 Key Points

- The standard of care for AML is rapidly evolving
  - Four new FDA approvals in 2017
    - Midostaurin - FLT3 inhibitor; (NEJM 2017; 377(5):454)
    - Daunorubicin and Cytarabine liposome (JCO 34, no.15_suppl May 2016)
    - Gemtuzumab ozogamicin - anti-CD33 antibody-drug conjugate (Leukemia 2017; 31(9):1855)
    - Enasidenib - IDH2 inhibitor (Blood 2017; 130(6):722)
- The need for cytogenetic and molecular analyses can present a challenge to the optimization of front-line therapy selection
- There is an evolving role of MRD analysis in the management of AML

Case 2

- 55 yo man with PMH including OA, RLS, OSA and Anxiety who presents with new L hip pain and AKI on labs completed by PCP
- Examination is remarkable for pain with ROM of the L hip; no other concerning findings noted
- Pertinent labs as follows:

Lab	Value
Creatinine	3.67 mg/dL
Ca	12.3 mg/dL
Hgb	9.8 g/dL
Albumin	3.9 g/dL
B2M	5.7 mg/L
LDH	120 U/L

Lab	Value
Kappa LC	4800 mg/dL
Lambda LC	6 mg/dL
K/L ratio	800
SPEP	No M-spike
IFE	Negative
UIFE	Kappa LC

Case 2

- BMBx is completed showing 30% monoclonal plasma cell population
  - MM FISH showed Del17p, Del 13q, Del 16q
- MRI Pelvis revealed a focal, 1 cm left pelvic lytic lesion
- A diagnosis of symptomatic multiple myeloma is confirmed
- R-ISS III based on Del 17p and B2M >5.5 mg/L
- Patient has an ECOG of 1 and is only limited by left hip pain and fatigue

Case 2

What therapy should be recommended for the this patient?

A. VRd + XRT to L Hip lesion

B. KRd + XRT to L Hip lesion

C. Clinical Trial + XRT to L Hip lesion

D. Rd + XRT to L Hip lesion

E. Daratumumab/Vd + XRT to L Hip lesion

Case 2

- Patient is started on VRd, which he tolerates well
- After 4 cycles, assessment of disease reveals a PR (>50% reduction on Kappa Light Chains)
- He is then assessed for transplant

Case 2

Considering the Del17p, what is the role of transplant at this time?

A. No role, continue with VRd and reassess response

B. Proceed to auto-HCT

C. Proceed to auto-HCT followed by allo-HCT

D. Proceed to tandem auto-HCT

E. No role, switch treatment regimen considering PR

Case 2

- Patient then proceeds with auto-HCT about 1 month after completion of Cycle 4 of VRd
  - Tolerates HCT, complicated only by neutropenic fever
- Reassessment of disease after engraftment and count recovery shows achievement of a CR

Case 2

What treatment strategy should be considered next?

A. Maintenance Lenalidomide

B. Maintenance Bortezomib

C. 2nd auto-HCT

D. Proceed to allo-HCT

E. Maintenance VRd

Case 2

- Patient is started on maintenance Lenalidomide and Zolendronic Acid
- Frequent assessment of disease shows continued CR
- At his assessment 1.5 years after transplant, his Kappa LC is noted to be rising once again along with new bone pain
  - He has no other signs of end-organ damage, but new symptomatic lytic lesions are found

Case 2

What treatment strategy should be initiated at this time?

A. Restart VRd

B. 2nd auto-HCT

C. VTD-PACE

D. KRd

E. Daratumumab-based regimen

Case 2

- Patient is restarted on VRd which improves his symptoms, but has no effect on his Kappa LC
- Patient then is the started on VTD-PACE x3, which helps him achieve a VGPR
- He then undergoes a second auto-HCT followed by maintenance Bortezomib
- Reassessment of disease by Kappa LC and BMBx shows a CR

Case 2

- Six months later, patient is noted to have rising Kappa LC once again along with new, symptomatic lytic lesions (FDG-negative) and no evidence of end-organ damage
- Patient is started on KRd
  - Reassessment of disease after 7 cycles shows he has achieved a CR
- At this time, he is an ECOG 1 with a good nutritional status and no significant complications from previous treatment/transplants

Case 2

What treatment option should be offered next?

A. Allo-HCT
B. Clinical Trial with CAR T-cell therapy
C. Continue KRd until progression
D. Maintenance therapy
E. Treatment Holiday

Case 2

- Patient is offered an allo-HCT as his brother is found to be a 10/10 HLA match
- He is admitted and given a Flu/Mel prep followed by stem cell infusion
  - His course is complicated by G4 GI GvHD requiring a 5+ month admission
- Patient is now two years post-transplant and doing well barring some chronic GvHD

Case 2 Key Points

- Induction with triplet novel agent therapy is the mainstay of frontline treatment for patients with multiple myeloma (Lancet 2017; 389 (10068):519)
- Autologous hematopoietic cell transplant followed by maintenance is recommended upfront for most transplant-eligible patients with a response to induction
  - Standard risk = Lenalidomide (JCO 2017; 35(29):3269)
  - Intermediate/High risk = Bortezomib (JCO 2012; 30(24):2946)
- Salvage novel agent therapy, second auto-HCT and allo-HCT can be utilized in the setting of previously treatment multiple myeloma

Case 3

- Patient underwent L adrenal mass biopsy showing CD20+, CD10-, BCL6+, BCL2+, MUM1- DLBCL with a Ki67 of 80%; FISH did not reveal any translocations but MYC was overexpressed by IHC
- BMBx completed and showed no evidence of disease
- Patient also found to have a large pericardial effusion, not FDG-avid on PET/CT; no tamponade physiology by TTE; she then underwent pericardiocentesis with no evidence of disease on cytology

Case 3

What regimen should be considered for MYC/BCL6 overexpression GCB-subtype DLBCL?

A. R-CHOP
B. DA-R-EPOCH
C. R-Hyper-CVAD
D. R-CODOX-M/IVAC
E. R-CHOP followed by Auto-HCT

Case 3

- What characteristics of her disease would warrant the addition of IT prophylaxis?

A. Disease on both sides of the diaphragm

B. MYC/BCL6 overexpression

C. Retroperitoneal involvement alone

D. LDH above upper limit of normal with >1 extranodal site

E. B and D

Case 3

- Patient then underwent DA-R-EPOCH with IT MTX
- PET/CT completed after 3 cycles shows a significant response with minimal disease activity
- Patient then completed 6 cycles of DA-R-EPOCH with IT MTX
- PET/CT after 6 cycles showed a CR

Case 3

Should upfront Auto-HCT be offered for this patient?

A. Yes, due to extent of disease

B. No, due achieving CR

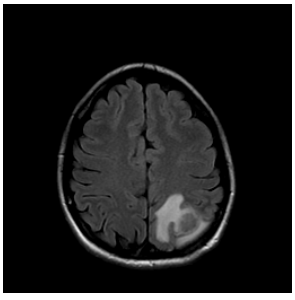
C. Yes, due to MYC overexpression

D. No, as the data is unclear

E. Yes, as the data is unclear

Case 3

- Auto-HCT was discussed with the patient and she decided to forgo transplant at this time
- She then started surveillance with H&P every 3 months
- Six months after completing treatment, the patient presented to an OSH ED with seizures
- MRI Brain was completed showing a large L parietal lesion; MR Spectroscopy and Perfusion were also completed, concerning for CNS relapse of Lymphoma
- LP was completed with negative cytology and flow; Bx not completed



Case 3

As further imaging did not reveal any other sites of disease, what regimen should the patient be offered next?

A. HD MTX + Ara-c

B. MTR

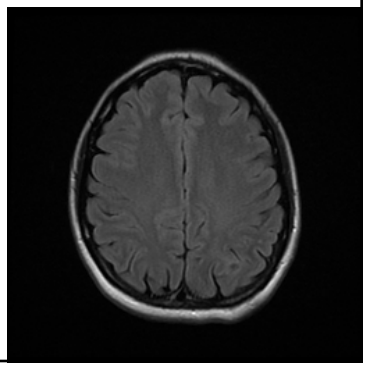
C. MATRix

D. MTR + WBRT

E. HD MTX alone

Case 3

- Patient was started on MTR
- After C3, patient underwent a repeat MRI showing a 50% decrease in the size of the mass
- After 6 cycles, patient showed a continued response
- She is overall doing well and tolerating therapy; ECOG 0



Case 3

- What is the role of transplant for this patient?

A. No transplant is warranted

B. Allo-HCT should be offered

C. No available data

D. Consolidative BEAM or Thiotepa-based Auto-HCT should be offered

E. EA consolidation should be offered

- Is there a role for XRT for this patient?

A. Yes, but only if she is not a transplant candidate

B. No role for XRT at all

C. Yes, but only as a palliative option

D. Yes, namely to improve response

Case 3

- Patient was offered a consolidative Auto-HCT with Rituximab/Thiotepa/Busulfan/Cyclophosphamide preparative regimen

Case 3 Key Points

- Patients with Double-hit DLBCL are known to have a poor prognosis; this is less clear of Double-expressor DLBCL but thought to be similar
- Response to R-CHOP is known to be poor; data for EPOCH is promising with CALGB/Alliance 50303 (subset) results still pending
- For CNS relapse, regimens with high-dose MTX or Cytarabine are reasonable with consideration of combinations (MTR, MATRix) as other options extrapolated from Primary CNS Lymphoma
- Due to poor long-term survival, high-dose chemotherapy followed by auto-HCT should be considered in young/fit patients (J Clin Oncol. 2015 Nov;33(33):3903-10)