Hematologic Malignancies Tumor Board 2020

Chair: Michaela Liedtke, MD
Associate Professor
Stanford Cancer Institute

Panel Members

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Bita Fakhri, MD, UC San Francisco	Panelist
David Iberri, MD, Stanford University	Panelist
Brian Jonas, MD, UC Davis	Panelist
Gabriel Mannis, MD, Stanford University	Panelist
Shahzad Siddique, MD, Dignity Health	Panelist
Jeffrey L. Wolf, MD, UC San Francisco	Panelist
Ilana Yurkiewicz, MD, Stanford University	Fellow

Case 1 - History

- 75 yo woman with germline BRCA2 mutation presenting with pancytopenia
- PMH notable for endometrial cancer and cervical cancer (2001) treated with TAH/BSO, radiation, cisplatin/5-FU, carbo/taxol, thalidomide, breast cancer (2011) treated with mastectomies, ddACT and radiation, and papillary serous carcinoma (2016) treated with carbo/taxol and niraparib
- SH: works full-time as an education researcher, lives alone, no children, former rare smoker, no EtOH/drugs
- Physical exam: well-appearing, no LAD, no splenomegaly, skin exam without petechiae or ecchymoses, neuro exam intact

Case 1 - Labs

- CBC: WBC 1.5, Hb 9.8, Hct 29.9, Platelets 62
- Differential: 11% PMNs (low), 8% bands, 72 lymphocytes (high), 5% monocytes, 4% eosinophils, no blasts
- CMP: Na 136, K 4.1, Cl 97, CO2 26, BUN 28, Cr 1.41 (baseline 1.1-1.4)
- Ca 9.4, Tbili 0.5, AST 18, ALT 18, Alk Phos 90

Case 1 – Work-Up

Bone marrow biopsy:

1. Acute myeloid leukemia **(AML)** involving 30-35% of bone marrow
2. Normocellular bone marrow with mild trilineage hypoplasia.
3. Negative for metastatic carcinoma.
4. FISH:
   - Del(5q): Detected.
   - Del(20q): Detected.
5. Cytogenetics: Abnormal female karyotype. 46,XX,der(7)t(1;7)(q12;q31),del(20)(q11.2q13.3),-21,+mar[4]/47,idem,del(1)(p13p22),+del(20)[8]/46,XX,del(5)(q15q33)[3]/46,XX[8]

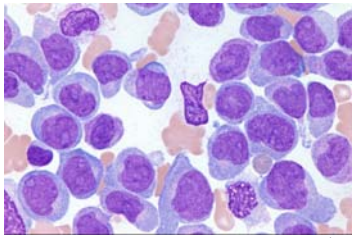


Image source: St Jude.

Echo: EF 65%

Case 1

What is the diagnosis?

A. AML with recurring genetic abnormality
B. AML with myelodysplasia-related changes
C. Therapy-related AML
D. AML, NOS

Case 1

Table 1. WHO classification of myeloid neoplasms and acute leukemia

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

Case 1 – t-AML

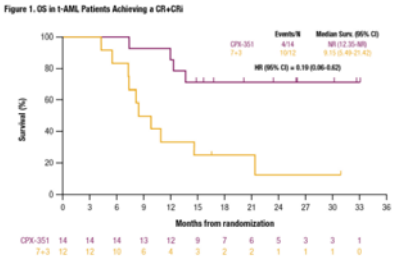
- Therapy-related myeloid neoplasms include t-AML and t-MDS
- Result of mutational events from cytotoxic therapy: chemotherapy, radiation, immunosuppressive therapy, or combination
- Unfavorable cytogenetics, such as a complex karyotype or deletion or loss of chromosomes 5 and/or 7, is considerably higher risk
- Outcomes historically poorer than in de-novo AML

What would you treat her with?

A) 7+3
B) CPX
C) Venetoclax + hypomethylating agent
D) Gemtuzomab

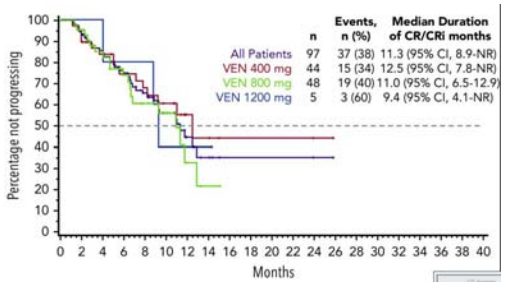
t-AML

- ASH 2019: 47% CPX and 36% 7+3 achieved CR+Cri
- Median OS was longer with CPX-351 vs 7+3 in t-AML pts who achieved a CR+CRi (not reached [NR] vs 9.15 mo; HR = 0.19)
- Cannot give if max adriamycin already given, as its cumulative



Source: Lancet et al. Outcomes in Patients with Therapy-Related Acute Myeloid Leukemia (t-AML) Who Achieved Remission with CPX-351 Versus 7+3: Phase 3 Exploratory Analysis.

Venetoclax + HMA for unfit patients



Cr +Cri rate: 67% in elderly patients with AML

DiNardo et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019.

Case 1: continued

- Started on decitabine dose reduced to 15 mg/m2 for CKD and venetoclax 400 mg daily
- Mid-cycle, hospitalized for fever, rash, joint swelling, though to be Sweet's syndrome. Resolved with steroid taper.
- After 2 cycles, morphologic CR1. MRD+ 0.2% blasts by flow
- Prior to Cycle 3, she is neutropenic

What would you do next?

A. Repeat bone marrow biopsy, assess for relapse
B. Continue with cycle 3 Ven/Dec
C. Give Neupogen, hold Ven/Dec for 1 week
D. Continue with Cycle 3, but dose reduce Venetoclax
E. Continue with Cycle 3, but dose reduce Decitabine
F. D and E

Case 1

- In Phase 1 study, among patients who have achieved MLFS of bone marrow, GCSF may be considered, with delay of cycle until neutrophil recovery >500
- If persists, consider reduce dosing schedule of venetoclax 3 weeks on/ 1 week off, followed by 2 weeks on / 2 weeks off if necessary
- If neutropenia continues, consider administer GCSF and dose reduce HMA by 50% (*DiNardo, Lancet Oncology 2018;19(2):216–228*)

Case 1: continued

- Continued Cycle 3, Ven was ultimately dose schedule reduced to 2 weeks on / 2 weeks off
- After 4 cycles, continues in CR1 but MRD positive by flow
- Evaluated by BMT, felt not a good candidate due to MRD positivity and age

Case 1: Take-Home Points

- t-AML is a distinct WHO classification associated with poor prognosis and complex cytogenetics
- If able to tolerate, CPX if preferable to 7+3 as intensive induction chemotherapy
- If unfit or maximum adriamycin already given, venetoclax/HMA is a good treatment strategy
- Ven/HMA main side effect cytopenias, guidelines on managing
- Evaluate for BMT, as this remains only curative option

Case 2: History and Labs

- 28 y/o man with no PMH presented with fatigue, weight loss (>15 lbs) and easy bruising
- PMH/PSH: asthma, recent tooth infection treated with antibiotics
- SH: student, aspiring physical therapist. No smoking, EtOH, drugs
- Physical exam: awake and NAD, no LAD, oropharynx with palatal petechiae, skin with petechial rash over bilateral arms, heart RRR, lungs clear to auscultation, neuro exam unremarkable
- Labs: WBC 35,000 with circulating blasts (50%), Hb of 4.7, Plts 17

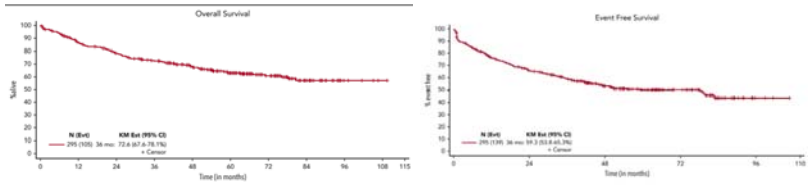
Case 2: Work-Up

- Flow cytometry of peripheral blood showed 84% abnormal blasts expressing partial CD34, CD10, CD19, TdT, partial CD20, partial CD22, CD79a, consistent with B lymphoblastic leukemia
- Bone marrow biopsy showed 97% involvement of B lymphoblastic leukemia
- Cytogenetics showed monosomy 21 and 7q-
- FISH was negative for BCR/ABL, RUNX1 amplification or MLL rearrangement

What would you treat with?

A) CALGB 10403
B) CALGB 9511
C) Hyper CVAD
D) other

Incorporation of pediatric regimens in adult ALL



Source: Stock et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood 2019.

Pediatric regimens vs adult regimens ALL

Feature	Pediatric Regimen	Adult Regimen
Asparaginase	Higher cumulative dose	Lower dose / no dose
Vincristine	Higher cumulative dose	Lower dose
Intrathecal therapy	Higher cumulative dose	Lowe dose
Steroid	High / similar cumulative dose	Lower or similar dose
Anthracycline	Lower cumulative dose	Higher dose
Cyclophosphamide	Lower cumulative dose	Higher dose
Cranial radiation	Variable / not recommended	Variable
Hospitalization	Induction only	Often with each cycle
Adverse effects	More asparaginase-related toxicities	More myelosuppression-related toxicities

Source: Muffly L and Curran E. Pediatric-inspired protocols in adult acute lymphoblastic leukemia: are the results bearing fruit? Hematology 2019.

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Case continued:

- At Day 28 after starting CALGB 10403, bone marrow biopsy showed persistent 23% blasts
- He then started on extended remission induction with doxorubicin, Peg-asparaginase, vincristine and prednisone
- Course complicated by disseminated candidiasis to skin and kidneys treated with caspofungin/fluconazole
- After one month, bone marrow biopsy showed no morphologic evidence of leukemia
- However, flow cytometry showed 1% population consistent with minimal residual disease (MRD)

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What next for morphologic CR with MRD positivity after induction?

A) Continue maintenance chemotherapy CALGB 10403 protocol
B) Change to blinatumomab
C) Change to inotuzumab
D) CAR-T
E) Proceed directly to allogeneic HCT

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Case 2: Role of MRD in ALL

- Assessment of MRD following frontline therapy should be performed in all ALL patients
- Presence of MRD after pediatric induction regimen and persistence after consolidation is extremely important prognostic feature
- In CALGB 10403 study, 44% were MRD negative at end of induction, with 3 year DFS 85%
- 53% were MRD positive, with 3 year DFS 54%
- Outcomes after allo BMT also superior after MRD negative

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Case 2: Blinatumomab as bridge to allo HCT

- In March 2018, the drug received accelerated FDA approval for treating ALL in first or second CR with positive MRD, defined as MRD ≥0.1 percent
- Based on phase 2 BLAST trial, in which patients ≥18 years old in first or later hematologic CR with MRD ≥0.1% were given blinatumomab with option of proceeding to HCT. Of 113 patients, 78% achieved a complete MRD negative response
- Used as bridge to achieve MRD negativity before transplant
- Administered as continuous infusion on 28 day cycle

Case continued

- On day 2 after starting blinatumomab at 9 mcg/day, febrile to 39, Tachy 130s, SBP 170s
- Blood cultures drawn, UA and CXR negative

What now?

A) Continue blinatumomab, give broad spectrum antibiotics
B) Continue blinatumomab, give IV Dexamethasone
C) Hold blinatumomab, give broad spectrum antibiotics
D) Hold blinatumomab, give IV Dexamethasone
E) Hold blinatumomab permanently

Case 2: Blina toxicities

Grade ≥3 adverse event of interest reported in at least 3% of patients in either group	
Neutropenia	101 (37.8)
Infection	91 (34.1)
Elevated liver enzyme	34 (12.7)
Neurologic event	25 (9.4)
Cytokine release syndrome	13 (4.9)
Infusion reaction	9 (3.4)
Lymphopenia	4 (1.5)

Source: Kantarjian et al. NEJM 2017.

Case 2: Blina real world toxicities

- CRS of any grade was reported in higher number of pts (94 [40%]) compared to clinical trials, though G3-4 CRS appears to be similar (G1-2 [36%], G3-4 [3%])
- Forty-four (44%) pts were treated with steroids and 8 (8%) pts required tocilizumab with steroids for CRS
- 93% had complete resolution of CRS
- CNS toxicities were observed in 55 (23%) pts, among them 17 (7%) had G3-4 toxicities
- Hepatic toxicities were observed in 83 (35%) pts
- Four (2%) pts died due to blinatumomab induced toxicities

Source: Badar et al. Real World Outcomes of Adult B-Cell Acute Lymphocytic Leukemia Patients Treated with Blinatumomab. Blood Advances, May 2020.

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Case 2: Managing Blina Toxicities

- Assess for and hold for grade III or greater neurologic toxicity or cytokine release syndrome
- For ***neurologic toxicity*** withhold until no more than grade I (mild) and for at least 3 days, then resume at 9 mcg/day x 7 days, then escalate dose to 28 mcg/day.
- If toxicity recurs on 9 mcg/day dose or resolution of symptoms takes longer than 7 days, discontinue drug permanently.
- For ***cytokine release syndrome*** withhold until grade 3 resolved, then resume at 9 mcg/day x 7 days, then escalate dose to 28 mcg/day if toxicity does not recur
- Dose escalation to 28 mcg/day should take place only after 7 days without toxicity-related event

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Case 2: continued

- After one cycle blina, bone marrow biopsy was MRD negative
- Course was complicated by fungal lesions in spleen and kidneys; thus BMT delayed and he received cycle 2 blina
- After cycle 2, MRD positive at 0.07%
- Received cycle 3 blina, MRD negative, underwent matched allogeneic BMT from sibling
- Post transplant course complicated by strep mitis bacteremia, disseminated candidiasis, acute cholecystitis s/p cholecystectomy, and CMV viremia
- MRD negative after transplant, remained in remission since, off all immunosuppression and without GVHD

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Case 2: Take-Home Points

- Pediatric regimen is safe and effective for young adults
- Persistent MRD after induction is strong prognostic feature and predicts worse outcomes after transplant
- Blinatumomab effective for treating MRD as a bridge to transplant
- Manage toxicities: CRS, neurotoxicity, hepatotoxicity
- Blinatumomab may also be used in relapsed/refractory setting, vs inotuzumab or CAR-T

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Case 3: History and Work-Up

- 71 year old man with PMH diabetes mellitus, Afib, HTN, severe aortic stenosis, stage 3 CKD, who presented for preoperative evaluation for shoulder surgery
- Pre-op labs showed CBC with WBC 39.4 (75% lymphocytes), Hb 14.9, platelets 358,000
- Flow cytometry of peripheral blood showed monoclonal B cell population with kappa light chain restriction positive for CD19, CD23, and CD5, consistent with CLL
- IGVH unmutated, FISH with deletion 11q and 13q

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Case 3: Continued

- Physical exam: no peripheral adenopathy
- Social history: retired warehouse supervisor
  - Former smoker, quit 2003. Former EtOH abuse (30 drinks/week), quit 2013. No drug use.
- Family history: no hematologic disorders or malignancies
- Diagnosed with Stage 0 CLL, recommended watchful waiting with repeat CBCs every 6 months

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Case 3: New Developments

- Doing well for 15 years, but then developed dyspnea on exertion and decreased exercise tolerance
- CBC showed Hb 7 (previously 11-12)
- Haptoglobin <8, LDH 427, spherocytes on peripheral smear, and IgG and C3 positivity on DAT. No bleeding.
- Diagnosed with Coombs' positive autoimmune hemolytic anemia (AIHA)
- Transfused 1 unit pRBC, started on prednisone 1 mg/kg
- WBC 310, plts 316

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What do you do?

A) Treat hemolytic anemia, for CLL continue watchful waiting
B) Start FCR
C) Start ibrutinib
D) Start venetoclax

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Case continued

- He starts ibrutinib 420 mg daily
- Re-admitted 1 week later with DOE, palpitations, dizziness, and leg swelling
- In Afib with RVR, responded to metoprolol, began TAVR work-up
- As part of TAVR work-up, underwent CT C/A/P showing multifocal ill-defined nodular opacities throughout the lung parenchyma

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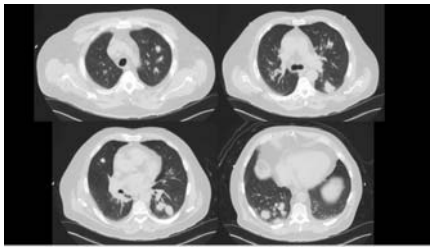
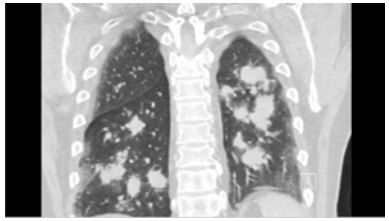
Case continued





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What do you do next?

A) Start empiric voriconazole
B) Start ceftriaxone and azithromycin
C) Start empiric Bactrim
D) Consult pulmonary for bronchoscopy with BAL

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Case continued

- Serum and BAL galactomannan were positive, serum beta D glucan was positive
- Multiple expectorated and BAL cultures grew >100 colonies of Aspergillus fumigatus
- Empirically started on isavuconazole (chosen over azoles due to less drug interaction with Ibrutinib, preferred over Ambisome due to less volume with renal failure)
- Also found to have hypogammaglobulinemia for which he received IVIG
- Prednisone for AIHA tapered off

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OIs in patients receiving ibrutinib for hematologic malignancies

Organism	Cases
Aspergillosis (pulmonary and/or CNS)	14
Cryptococcus	1
Cytomegalovirus	1
Histoplasmosis	1
Listeria	1
Mycobacterium avium intracellulare, pulmonary	1
Mycobacterium tuberculosis, CNS	1
Nocardiosis	1
Pneumocystis jirovecii pneumonia	6
Varicella zoster	15

Tillman BF, et al. Eur J Haematol 2018

Ibrutinib and opportunistic infections

- "Consider prophylaxis according to standard of care in patients who are at increased risk for OIs"
- PCP prophylaxis: prednisone ≥20 mg/d (or equivalent) for ≥4 weeks
- Consider mold prophylaxis especially if also on steroids
- Ibrutinib dose-adjustment (based on antifungal agent):
  - posaconazole 300 mg po q24h = ibrutinib 70 mg po q24h
  - voriconazole 200 mg po q12h = ibrutinib 140 mg po q24h
  - isavuconazole 372 mg po q24h = ibrutinib 280 mg po q24h

Case continued

- Several months later, developed recurrent hemolysis with Hb 7.2, re-started on 60 mg prednisone
- Hospitalized with GIB, AVM clipped, temporarily held ibrutinib
- Several months later, admitted for recurrent GI bleeding, confusion, worsening CT chest, and new frontal/temporal lobe lesions
- There was concern that the brain lesions were due to a fungal infection (possibly aspergillosis given history of pulm aspergillosis)
- Pt and wife did not want brain biopsy or other highly invasive procedures
- Discussion regarding the difficulty of treating with ambisome due to its nephrotoxicity and its need for high-volume hydration – especially difficult given his history of CKD and HFrEF
- Pt and his wife opted for home with hospice

Case 3: Take-Home Points

- Standard of care first line therapy has now moved to targeted oral agents for both younger and older patients with newly diagnosed CLL
- Ibrutinib treatment is indefinite and associated with fungal pneumonia, Afib, and GI hemorrhage
- Strongly consider fungal prophylaxis if patient also on steroids such as in AIHA
- Ibrutininb and azoles interact via CYP clearance, requiring dose adjustment of ibrutinib

Case 4: History

- 56 year old man, presented to PCP with gradual exercise intolerance
- PMH: asthma, prior intubation for severe asthma flare
- SH: professional sports commentator, married with two children, no smoking, EtOH, drugs
- Physical exam: no acute distress, lungs clear to auscultation, no bony pain on palpation, no LAD, RRR

Case 4: Labs

- WBC 5.3, Hgb 9.9, Plts 158, MCV 104, ANC 1320
- Na 132, Cr 1.65, albumin 2.7, total protein 13.2, globulin 10.5
- SPEP showed presence of M spike at 8.3 g/dL
- Serum light chains showed elevated kappa light chain at 294 mg/dl, lambda light chain 0.2 g/dl, ratio 1,470
- UPIE with abnormal band identified as monoclonal kappa light chain (Bence-Jones protein)

Case 4: Work-Up

Bone marrow biopsy:

- Infiltration of bone marrow by 87% plasma cells with reduced trilineage hematopoiesis
- Cytogenetics: abnormal clonal karyotype with monosomy #13 and 1q copy gain
- FISH: t(11;14) translocation

Skeletal survey: no lytic lesions

What treatment do you start?

A) VRD (Velcade, Revlimid, Dexamethasone)
B) KRD (Carfilzomib, Revlimid, Dexamethasone)
C) RD (Revlimid, Dexamethasone)
D) Autologous transplant

Case 4: Continued

- Started one cycle VRD (this was before cytogenetics/FISH became available), M spike increased
- Once high risk disease confirmed, switched to KRD
- After 7 cycles, proceeded to autologous HCT
- After HCT, bone marrow biopsy with 5% plasma cells, M spike 1.2, kappa light chain 53

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Which of the following co-morbidities would make you *not* start KRD?

A) Hyperglycemia
B) Osteoporosis
C) Congestive heart failure
D) Depression

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Carfilzomib and cardiac toxicity

- Second generation proteasome inhibitor
- Per meta-analyses overall risk of cardiotoxicity 8.7% and 4.9% for grade 3 or above (*Shah et al, Leuk Lymphoma 2018*)
- Reported events include CHF, ischemic heart disease, arrhythmia, sudden cardiac arrest

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Skeletal surveys are negative. Cr is normalized. What do you do about bone modifying agents?

A) Not needed without lytic lesions
B) Start Zoledronic acid, continue indefinitely
C) Start Zoledronic acid, with an end date
D) Start Denosumab, continue indefinitely
E) Start Denosumab, with an end date

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Bone Modifying Agents in MM

- Bisphosphonates are an essential part of the management of active symptomatic MM, with or without lytic lesions
- Bone modifying agents to dot repair existing bone damage, but prevent development of new lesions
- Denosumab is non-inferior to zoledronic acid for time to skeletal-related events (*Raje et al. Lancet 2018*)
- When CrCl <30, denosumab preferred because it is not renally cleared
- Duration of treatment: up to 2 years per ASCO guidelines 2018

Case 4: continued

- 18 months after starting maintenance, M-spike rises to 1.9, concerning for biochemical relapse
- No signs of clinical progression

What next?

- Daratumumab/velcade/dexamethasone
- Daratumumab/pomalidomide/dexamethasone
- Elotuzumab/dexamethasone
- Pomalidomide/dexamethasone

Three drug regimens for relapsed MM

- When possible, 3 drugs preferred over 2 drugs, as addition of third agent improves PFS and OS
- Try to incorporate at least 2 new drugs patient has not seen

Case 4: continued

- He tolerated dara/pom/dex well, with improvement in his M spike
- Completed 2 years of zoledronic acid, without osteopenia or bony lesions
- He continues on dara/pom/dex today with good overall quality of life

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Case 4: Take-Home Points

- Initial treatment strategies for high-risk multiple myeloma include VRD and KRD
- Risk of cardiotoxicity (particularly CHF) with Carfilzomib, ~5% per meta-analyses
- With or without lytic lesions, bone modifying agent should be introduced, for up to 2 years, with denosumab preferred when renal insufficiency present
- At time of relapse, three drug regimen preferred over two drug regimen

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