Case Presentations:
Leukemia, Lymphoma, and Myeloma

Association of Northern California Oncologists

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Case 1:
"48 year old man presenting with persistent tearing from his left eye"

Presented with persistent tearing from his left eye for the past 1-2 months and double vision for the past week. On review of system, he denied fever, night sweats, weight loss, headache, epistaxis.

Past Medical History:

- No major comorbidities

Family History:

- Noncontributory

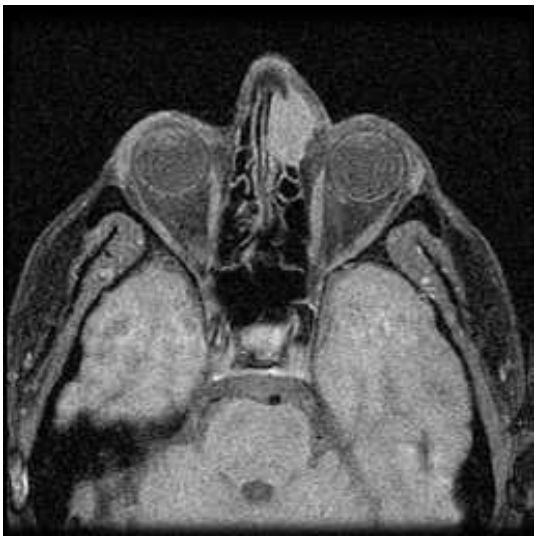
Social History:

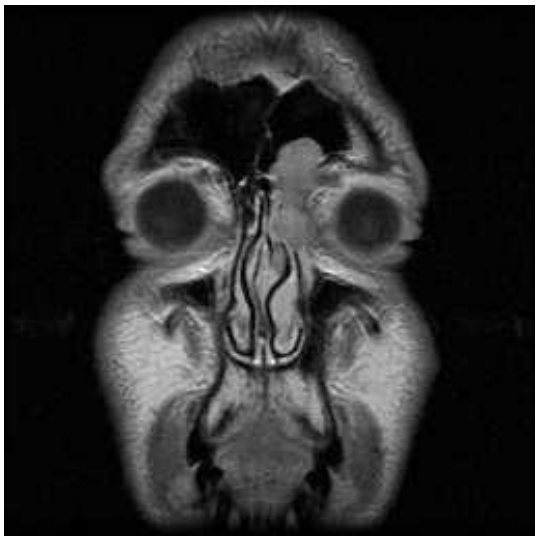
- He is married and works as an animator for Pixar.
- He smokes 1 pack/day for past 25 years. He does not drink alcohol or use illicit drugs.

Physical Exam:

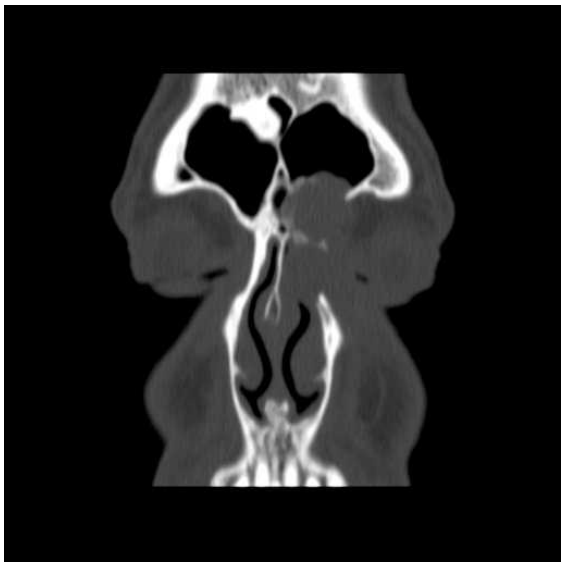
- Gen: Well-appearing, well-nourished, no acute distress
- HEENT: Normocephalic, pupils equally round & reactive to light. No orbital swelling or asymmetry of the eyes. Extraocular muscles intact.
- CV: Regular rate & rhythm, normal heart sounds
- Pulm: Clear to auscultation bilaterally, no wheezes/rales/rhonchi. No chest wall tenderness.
- Lymph: No cervical, supraclavicular, axillary, or inguinal adenopathy
- Abd: soft, non-tender, no hepatosplenomegaly
- Extremities: No cyanosis or edema, pulses 2+
- Neuro: A&Ox4, no focal neurologic deficits
- Skin: no rashes, ecchymosis, petechiae

MRI orbits with contrast:





CT sinuses without contrast:



Biopsy of left nasal cavity mass:

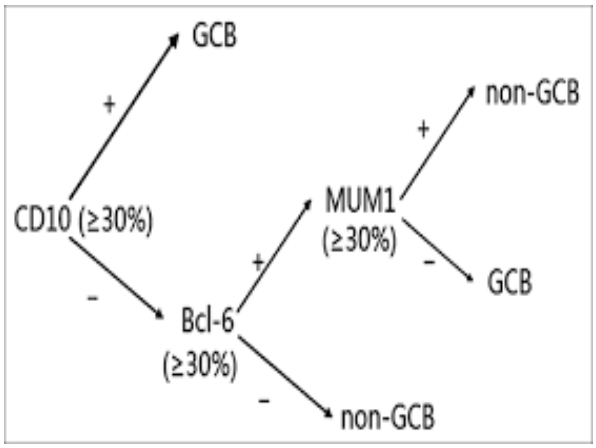
Diffuse large B-cell lymphoma

Expert Discussion: Dr. Joseph Tuscano

- *What would be your initial workup?*

IHC stains & FISH results

- IHC staining
  - Positive for BCL-2, BCL-6, MUM-1, C-MYC (>40%)
  - Negative for CD5 and CD10
- FISH panel: Negative for MYC, BCL-2, BCL-6 translocations



Labs:

- WBC 7.4
- Hgb 15.1
- Hct 44.4
- Plt 249

- Na 137
- K 4.2
- Cl 101
- HCO3 29
- BUN 18
- Cr 1.06
- Ca 9.1
- LDH 165

- HIV Ab negative
- Hep B surface Ag negative
- Hep B total core Ab negative
- Hep C Ab negative

Additional Work-up:

- PET/CT:
  - Destructive soft tissue mass involving the **left nasal bone and medial orbit extending into the frontal and ethmoid sinus** measuring 2 x 2.5 cm. **SUVmax = 18.8.**
- CSF cytology and flow cytometry:
  - Negative for lymphoma
- Bone marrow biopsy:
  - Negative for involvement by lymphoma

Diagnosis:

Stage IAE DLBCL, double expressor, non-GCB subtype

Revised IPI score of 0

Expert Discussion: Dr. Joseph Tuscano

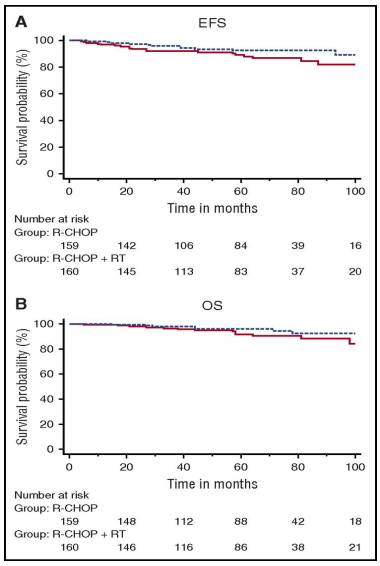
- *How would you treat this patient?*
- *What is the role for radiation?*
- *Would you recommend CNS prophylaxis?*

Clinical Course

- He was treated with R-CHOP x 6 cycles plus IT methotrexate x 4
  - Vincristine was dose-reduced by 50% for cycles 4-6 due to neuropathy.
- Post-treatment PET/CT showed metabolic complete response.
- He went on to receive 3 cycles of high-dose methotrexate 3 grams/m^2 for CNS prophylaxis.

Limited stage DLBCL

- Standard treatment is abbreviated course of RCHOP x 3 followed by XRT
- Recent studies suggest that RCHOP x 4-6 cycles alone is not inferior to RCHOP followed by XRT for non-bulky limited stage DLBCL.
- The only phase III trial comparing R-CHOP vs. R-CHOP + XRT reported similar outcomes: 5-yr EFS 89% vs 92%, 5-yr OS 92% vs 96%, respectively.

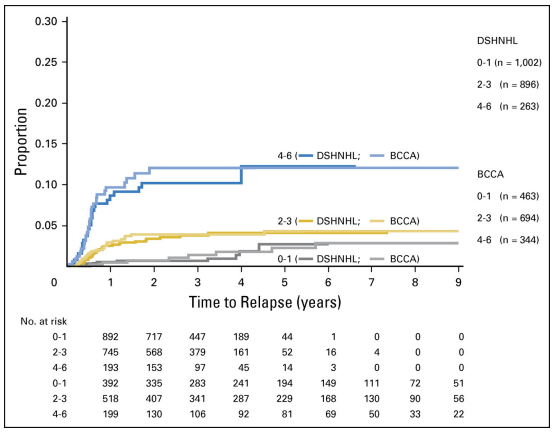


Thierry Lamy et al. Blood 2018;131:174-181

Solid line, R-CHOP; dotted line, R-CHOP plus RT

CNS International Prognostic Index (CNS-IPI) predicts risk for CNS relapse

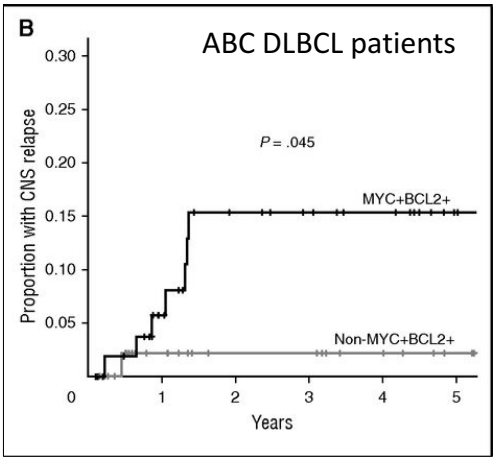
- CNS-IPI score:
  - Age > 60 years
  - ECOG > 1
  - Elevated LDH
  - Extranodal involvement > 1 site
  - Stage III/IV disease
  - Kidney or adrenal gland involvement
- 2-yr rates for CNS disease
  - Low-risk (0-1) → 0.6%
  - Intermediate-risk (2-3) → 3.4%
  - High-risk (4-6) → 10.2%



Schmitz et al. Clin Oncol 2016;34:3150-3156

Dual expression of MYC and BCL2 predicts CNS relapse in DLBCL

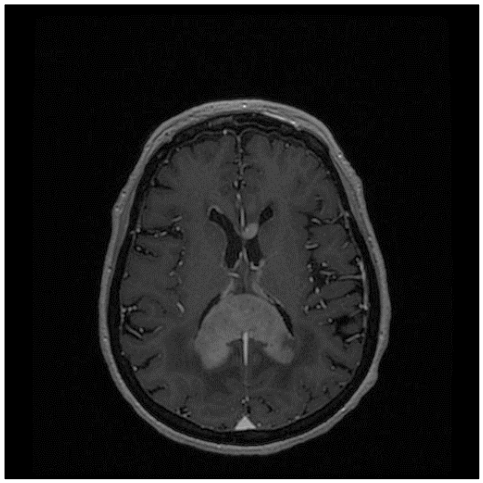
- Dual expression of **MYC** and **BCL2** is associated with an increased risk of CNS relapse in DLBCL treated with R-CHOP.
- With a median follow-up of 6.8 years, risk of CNS relapse was higher in double expressors compared to non-double expressors (**2-yr risk, 9.7% vs 2.2%;** p = .001).
- Patients with **non-GCB DLBCL** have an increased risk of CNS relapse (2-year risk, 7.1% vs 2.2%; p = .02).



Savage et al. Blood 2016;127:2182-2188

High-dose methotrexate as CNS prophylaxis

- There is a propensity for parenchymal involvement in secondary CNS relapse in DLBCL.
- IT chemotherapy might not be the ideal strategy for CNS prophylaxis.
- High-dose methotrexate can deeply penetrate all CNS compartments.



Studies evaluating HD-MTX for CNS ppx in DLBCL

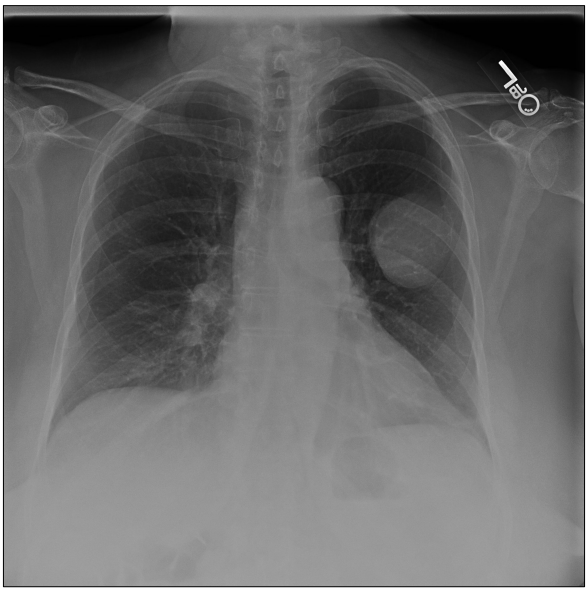
Study	Study type	Lymphoma type/risk	Primary treatment	Systemic CNS prophylaxis (# cycles)	CNS relapse
GELA/LYSA, Tilly et al[40]	Prospective phase 3	All aggressive 80% DLBCL	1. ACVBP 2. CHOP	1. HDMTX 3 g/m^2 (2) 2. None	0.8%* 2.7%* $P = .002$
Nordic, Holte et al[41]	Prospective phase 2	DLBCL (74%) FL 3A aaIPI 2-3	DI R-CHOEP14	AraC 3 g/m^2 (1) HDMTX 3 g/m^2 (1)	4.4%*
UK NCRI/Bloodwise, Phillips et al[42]	Prospective phase 2	DLBCL IPI ≥3	R-CODOX-M-R-IVAC	HDMTX 3 g/m^2 (+IT) Ifosfamide, AraC (+IT)	All 4.6% (2 y) 0 intermediate-risk CNS-IPI 6.2% high-risk CNS-IPI
US-MGH, Abramson et al[43]	Retrospective	DLBCL High CNS risk†	R-CHOP (97%)	HDMTX 3-3.5 g/m^2 (3)	3%*
Australia, Cheah et al[44]	Retrospective	DLBCL High CNS risk‡	1. CHOP(-like) ± R§ 2. CHOP(-like) ± R 3. Dose-intense	1. None (IT alone) 2. HDMTX 1-3 g/m^2 (2) 3. HDMTX 1-3 g/m^2 (2) (+IT)	1. 18.4% (3 y) 2. 6.9% (3 y) 3. 2.3% (3 y) $P = .009$
Italy, Ferreri et al[45]	Retrospective	DLBCL High CNS risk¶	R-CHOP	None HDMTX 3 g/m^2 ± IT	12%* 0

Hematology Am Soc Hematol Educ Program 2017;2017(1):578-586

Teaching Points

- R-CHOP alone x 4-6 cycles is not inferior to R-CHOP + XRT for limited stage DLBCL.
- CNS-IPI score and double expression of MYC and BCL2 predict risk of CNS relapse in DLBCL.
- High-dose methotrexate might be more effective than IT methotrexate for CNS prophylaxis.

Case 2:
"64 year old woman presenting with an abnormal CXR"



Presented to PCP for pre-op evaluation for a right knee replacement. She underwent a routine CXR which incidentally found a 6.1 cm left upper lobe lung mass. On review of system, she denied shortness of breath, cough, chest pain, fever, night sweats, and weight loss.

Past Medical History:

- Knee osteoarthritis, hypertension, type II diabetes

Family History:

- Mother- breast cancer

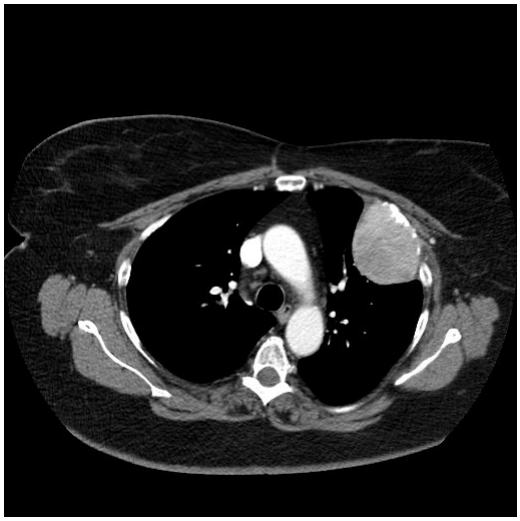
Social History:

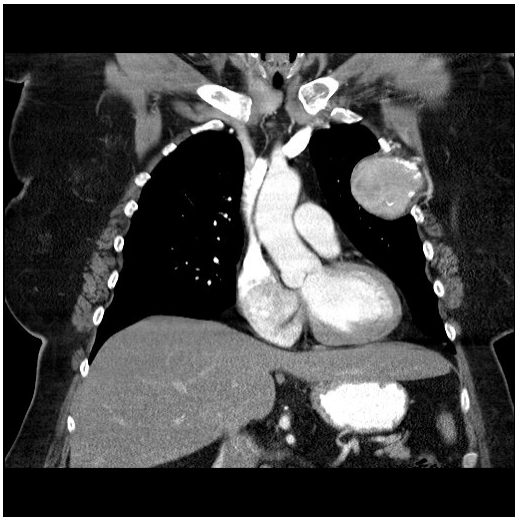
- She is married and retired.
- She does not smoke, drink alcohol, or use illicit drugs.

Physical Exam:

- Gen: Well-appearing, well-nourished, no acute distress
- HEENT: Normocephalic, pupils equally round & reactive to light
- CV: Regular rate & rhythm, normal heart sounds
- Pulm: Clear to auscultation bilaterally, no wheezes/rales/rhonchi. No chest wall tenderness.
- Abd: soft, non-tender, no hepatosplenomegaly
- Extremities: No cyanosis or edema, pulses 2+
- Neuro: A&Ox4, no focal neurologic deficits
- Skin: no rashes, ecchymosis, petechiae
- MSK: No spinal tenderness

CT chest:





CT-guided core needle biopsy of mass:

Sheets of monoclonal plasma cells, kappa light chain restricted

Cytogenetics & Molecular Studies:

Cytogenetics:

46, XX

Molecular Studies:

- Positive for t(11;14)
- Negative for 17p13 deletion
- Negative for gain of 1q21

Expert Discussion: Dr. Jeffrey Wolf

- *What would be your initial workup?*

Labs:

- WBC 9.3
- Hgb 14.5
- Hct 43.3
- Plt 265

- Na 139
- K 3.8
- Cl 105
- HCO3 26
- BUN 18
- Cr 0.91
- Glucose 146
- Ca 9.8
- LDH 111

- IgA 40 (low)
- IgG 637 (low)
- IgM 19 (low)
- β2M 3.05 mg/L (high)
- Serum IEP: negative
- FKLC 278.2 mg/L
- FLLC 9.1 mg/L
- FLC ratio 30.6

- Urine IEP: very faint KLC
- Urine protein: 24 mg/dL
- Urine Cr: 284.4 mg/dL
- Urine protein/Cr: 0.08

Imaging & Bone marrow biopsy:

- PET/CT:
  - No evidence of disease anywhere else besides the left lung mass

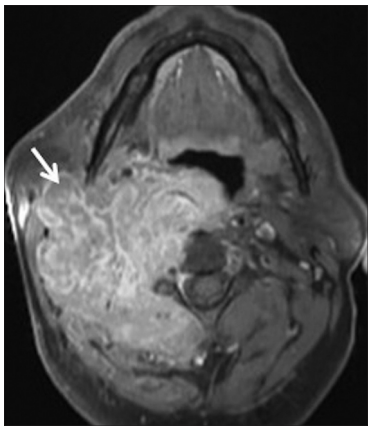
- Bone marrow biopsy:
  - No clonal plasma cells by morphology
  - **Multiparameter flow cytometry detects a clonal population of kappa light chain-restricted plasma cells (5%)**

Diagnosis:

Solitary bone plasmacytoma with minimal bone marrow involvement

Solitary Plasmacytoma

- Single mass of clonal plasma cells with no or minimal bone marrow plasmacytosis
- Rare disease that represents 5-10% of all plasma cell neoplasms
- Extramedullary plasmacytoma (EMP) vs. solitary bone plasmacytoma (SBP)
- Solitary plasmacytoma with minimal bone marrow involvement → monoclonal plasma cell infiltration < 10% in bone marrow



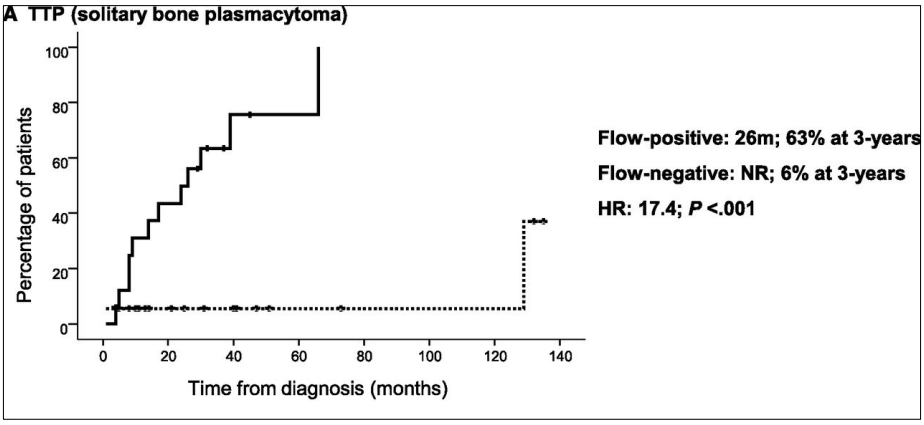
Indian J Radiol Imaging 2014;24:410-4

Prognostic Factors

RISK FACTORS	RISK OF PROGRESSION TO MYELOMA
Solitary bone plasmacytoma (SBP)	SBP patients have higher risk for progression compared to EMP patients: **10-yr progression rate 65-85% vs. 25-35%**
Bone marrow plasmacytosis detected by flow cytometry	Minimal bone marrow involvement is associated with decreased progression-free survival
Abnormal serum FLC ratio	Abnormal serum FLC ratio is associated with a higher risk of progression compared to a normal SFLC ratio**: 5-yr progression rate 44% vs. 26%**
Persistence of a serum monoclonal protein after treatment	Persistence of M protein > 1 year after XRT associated with higher risk of progression compared to resolution of M protein: **10-yr progression rate 71% vs. 9%**

Caers et al. Journal of Hematology & Oncology (2018) 11:10

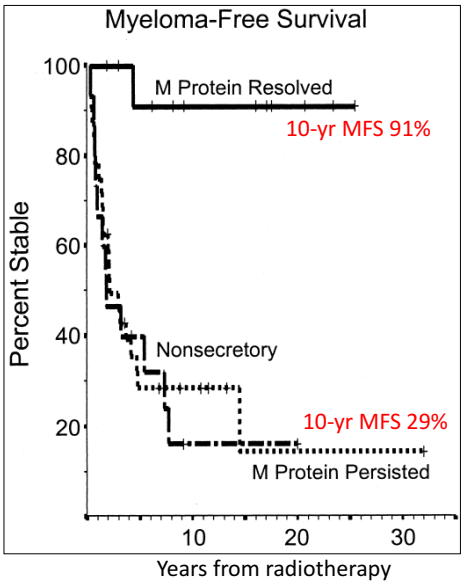
Time to progression to myeloma according to sensitive multiparameter flow cytometry on bone marrow



Bruno Paiva et al. Blood 2014;124:1300-1303

Persistent M protein after XRT

- 60 patients at M.D. Anderson with SBP treated with XRT alone (median, 46 Gy)
- On multivariate analysis, persistence of M protein > 1 year after XRT was only independent prognostic factor for myeloma-free survival (p=0.005) and cause-specific survival (p=0.04)
- Most patients with persistent M protein following XRT developed myeloma within 2.2 years of treatment.



Wilder et al. Cancer 2002;94:1532–7.

Expert Discussion: Dr. Jeffrey Wolf

- *How would you treat this patient?*
- *What is the role of chemotherapy and autologous stem cell transplant (ASCT)?*

Adjuvant chemotherapy and ASCT for plasmacytoma

Study	Treatment	Patients	Outcomes
Retrospective (Holland et al, 1992)	**Adjuvant chemotherapy**	46 pts with SBP or EMP	Chemo did not affect incidence of progression to MM but **delayed progression from 29 to 59 mo**
Retrospective (Mheidly et al, 2016)	**XRT vs. combined XRT + chemotherapy**	52 pts with SBP	5-year PFS rate in the XRT group was 27.5% vs. 53.6% in the combined treatment group (p=0.31)
Case series (Jantunen et al, 2005)	**ASCT**	12 pts with high-risk plasmacytoma	After median follow-up of 48 mo after ASCT, 11 (92%) alive, 6 (50%) relapsed or progressed after ASCT

Clinical Course

- She underwent radiation (30 Gy) over 4 weeks to the left lung mass and received concomitant chemotherapy: VRd (Velcade, Revlimid, Decadron); cycle length 21 days.
- Received 8 cycles of VRd with near complete resolution of lung mass, normalization of FLC ratio, and negative immunofixation in the urine.
- She was started on maintenance lenalidomide but was lost to follow-up.

Clinical Course

- Twelve months later, she presented with progressive fatigue and acute renal insufficiency.
- Serum Cr 3.03 (baseline 1.2)
- M-spike 4.7 g/dL
- IgG level 5143 mg/dL
- Free kappa light chain: 2376 mg/L
- Free lambda light chain: 2.3 mg/L
- FLC ratio 1033

Expert Discussion: Dr. Jeffrey Wolf

- *How would you treat this patient?*
- *What is the role for intensive chemotherapy (ie. hyperCAD + proteasome inhibitor)?*

Clinical Course

- She underwent plasmapheresis and received 1 cycle of hyperCD + carfilzomib.
  - Cyclophosphamide 350 mg/m^2 IV q12 hrs on days 1-3
  - Dexamethasone 40 mg PO daily on days 1-4, 8-11, 15-18
  - Carfilzomib 20 mg/m^2 IV on days 1, 8, and 15
- On day 12, repeat M-spike was 1.6 g/dL and free KLC was 990 mg/L.
- She was switched to an outpatient regimen (CyBorD).

UCSF experience with modified Hyper-CVAD + proteasome inhibitor

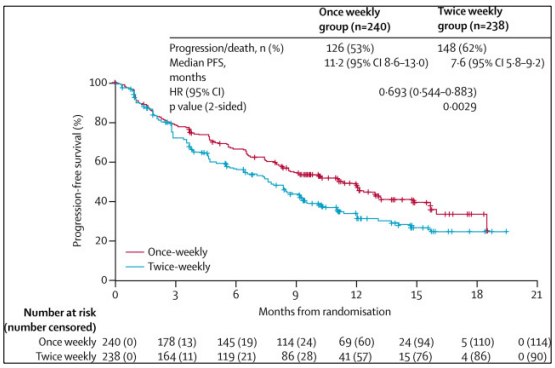
- Retrospective study of 67 MM patients who received at least 1 cycle of hyper-CD in the setting of renal insufficiency (eGFR < 50 mL/min)
- Treatment:
  - Cytoxan 350 mg/m^2 q12 hrs on D1-3
  - Doxorubicin 10 mg/m^2 on D1-3
  - Dexamethasone 20-40 mg on D1-4, D8-11, D15-18
  - Bortezomib or carfilzomib at standard dose
- 8 of 23 patients (35%) were able to discontinue dialysis.
- Median % improvement in creatinine in non-dialysis patients was 24%.
- Median PFS was 5.1 mo.

Response Category	N = 67
Complete Response	1%
Very Good Partial Response	28%
Partial Response	39%
Overall Response Rate	**69%**

Galligan et al. Blood. 2018 Dec;3236

Once weekly vs. twice weekly carfilzomib

- Randomized phase 3 A.R.R.O.W. trial of once weekly carfilzomib 70 mg/m^2 vs. twice weekly carfilzomib 27 mg/m^2 vs in pts with R/R MM
- Weekly carfilzomib arm: 20 mg/m^2 on D1, 8, and 15 of C1; 70 mg/m^2 thereafter
- Median PFS was 11.2 mo. in the once weekly group compared to 7.6 mo. In the twice weekly group (p=0.0029)
- Overall safety was similar between the groups with incidence of ≥ grade 3 heart failure of 3-4% in both groups



Moreau et al. Lancet Oncol. 2018 Jul;19(7):953-964

Teaching Points

- Solitary plasmacytoma with evidence of bone marrow involvement has high risk for progression to myeloma and systemic treatment should be considered.
- Hyper-CAD + proteasome inhibitor is an effective cytoreductive therapy for myeloma with high tumor burden or aggressive presentation.
- Weekly carfilzomib 70 mg/m^2 is as effective as twice weekly carfilzomib and could be more convenient for patients & providers.

Case 3:
"62 year old woman presenting with fatigue and dyspnea on exertion"

Presented with 1 month of progressive fatigue and dyspnea on exertion. On review of system, she denied fever, night sweats, and weight loss.

Past Medical History:

- Right-sided stage II node-negative breast invasive ductal carcinoma (ER+, PR+, HER2-) diagnosed 8 years ago
  - S/p right mastectomy
  - Adjuvant docetaxel + cyclophosphamide x 4 cycles
  - Letrozole x 5 years

Family History:

- Noncontributory

Social History:

- She is divorced and retired.
- She does not smoke, drink alcohol, or use illicit drugs.

Physical Exam:

- Gen: Well-appearing, well-nourished, no acute distress
- HEENT: Normocephalic, pupils equally round & reactive to light
- CV: Regular rate & rhythm, normal heart sounds
- Pulm: Clear to auscultation bilaterally, no wheezes/rales/rhonchi
- Abd: soft, non-tender, no hepatosplenomegaly
- Lymph: No cervical, supraclavicular, axillary, or inguinal adenopathy
- Extremities: No cyanosis or edema, pulses 2+
- Neuro: A&Ox4, no focal neurologic deficits
- Skin: no rashes, ecchymosis, petechiae

Labs:

- WBC 3.3
- Hgb 10.4
- MCV 114
- Plt 282
- ANC 0.58
- Reticulocyte 2%
- Ferritin 139 ug/L
- Serum iron 135 ug/dL
- Transferrin 182 mg/dL
- % saturation 53%
- Vitamin B12 1245 ng/L
- Serum folate 15 ng/mL

Bone marrow biopsy results:

Acute myeloid leukemia with 31% blasts

No overt dysplasia

Cytogenetics & Molecular Studies:

Cytogenetics:

46, XX

Molecular Studies:

- Positive for RUNX1 mutation
- Negative for FLT3-ITD or FLT3-TKD mutation
- Negative for *NPM1* mutation
- Negative for CEBP *alpha* mutation

Expert Discussion: Dr. Tian Zhang

- *How would you risk stratify this patient?*
- *How would you treat this patient?*

Clinical Course

- She received Vyxeos (100 mg/m2 cytarabine and 44 mg/m2 daunorubicin) administered on days 1, 3, and 5
- Developed neutropenic fever during chemotherapy: received vancomycin, cefepime, voriconazole, and acyclovir
- Day 14 bone marrow biopsy: Hypocellular marrow (5% cellularity) with < 5% blasts

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JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ryan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur C. Louie, and Bruno C. Medeiros

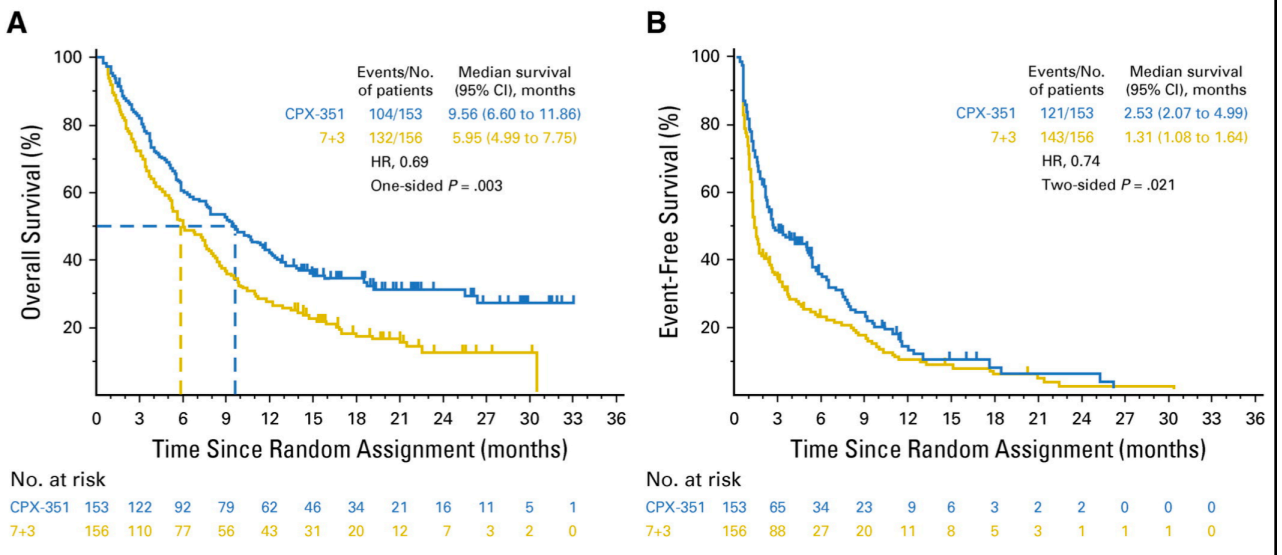
Treatment Arms (1:1 randomization)

- Per protocol: ≤ 2 inductions, ≤ 2 consolidations
  - Induction response measured with day 14 bone marrow biopsy
  - Reinduction if CR or Cr_i (CR without count recovery) not achieved
- Choice of subsequent alloHCT per treating physician

Drug dosing	Induction*	Consolidation
CPX-351	100 U/m^2 CPX-351 (100 mg/m2 cytarabine, 44 mg/m2 daunorubicin) on D1,3,5	65 U/m^2 CPX-351 (65 mg/m2 cytarabine, 29 mg/m2 daunorubicin) on D1,3
Control	7+3 [cytarabine D1-7; daunorubicin D1,2,3]	5+2 [cytarabine D1-5; daunorubicin D1,2]

**Reinduction if no CR: 100 U/m^2 CPX-351 D1,3; or 5+2*

Survival Outcomes



Lancet et al. J Clin Oncol 36:2684-2692

Bone marrow biopsy at 5 weeks post-Vyxeos

Hypocellular marrow (20-30% cellularity) with **5% blasts**

Flow cytometric evidence of mildly abnormal blast population (2.1%)

Expert Discussion: Dr. Tian Zhang

- *How would you treat this patient?*

Clinical Course

- She received re-induction treatment with Vyxeos (100 mg/m2 cytarabine and 44 mg/m2 daunorubicin) administered on days 1 and 3
- Bone marrow biopsy at 4 weeks showed normocellular marrow with <5% blasts and MRD-negative by flow.
- She proceeded with matched related donor allogeneic hematopoietic cell transplant.

Clinical Course

- Bone marrow biopsy at day +100 showed **relapse with 30% blasts.**
- NGS studies showed no targetable mutations.

Expert Discussion: Dr. Tian Zhang

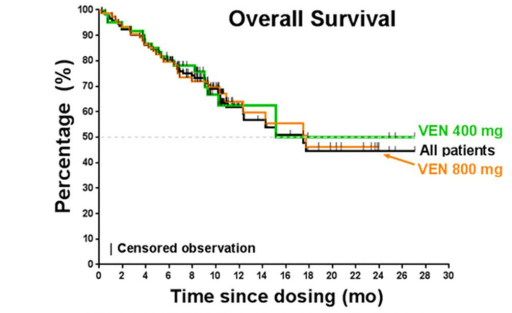
- *Other than a clinical trial, how would you treat this patient?*

Clinical Course

- She was started on venetoclax 400 mg plus decitabine 20 mg/m^2 x 10 days.
- Bone marrow biopsy at day 28 showed complete remission with < 5% blasts.

Venetoclax + Hypomethylating Agent (HMA) in untreated AML

- Phase Ib study of 145 pts ≥ 65 yrs with untreated AML ineligible for intensive chemotherapy
- **Venetoclax** 400, 800, or 1200 mg QD PLUS
  either **azacitidine** 75 mg/m^2 x 7 days
  or **decitabine** 20 mg/m^2 x 5 days



Group	n	CR/CRi n (%)	Median (months) Duration of CR/CRi	Median (months) OS
All patients	145*	95 (66)	11.0	17.5
VEN 400 mg	60	44 (73)	11.0	NR
+ AZA	29	22 (76)	NR	NR
+ DEC	31	22 (71)	11.7	15.2
VEN 800 mg	74	46 (62)	11.7	17.7
+ AZA	37	21 (57)	11.7	14.2
+ DEC	37	25 (69)	6.8	17.7

*Includes 11 patients who received VEN 1200 mg patients.
NR, not yet reached.

DiNardo et al. Blood 2017 130:2628

Venetoclax + HMA in relapsed/refractory AML

City of Hope, Retrospective study, 33 patients with R/R AML

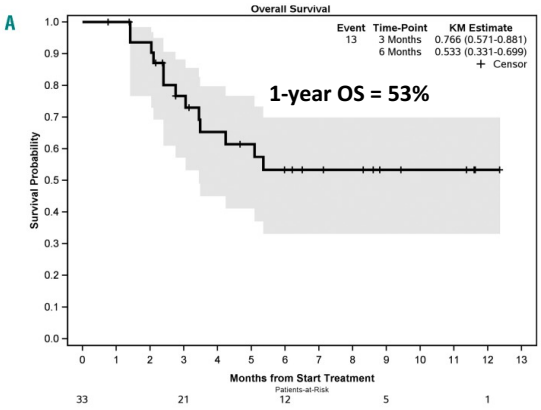
Table 1. Patients' characteristics.

	Total (n=33)
Age	
Median	62.0
Range	(19.0-81.0)
Sex	
Male	15 (45.5%)
Female	18 (54.5%)
AML type	
De novo	23 (69.7%)
Secondary	5 (15.2%)
Therapy-related	5 (15.2%)
Cytogenetic/molecular risk*	
Good	3 (9.1%)
Intermediate	11 (33.3%)
High	18 (54.5%)
Unknown	1 (3%)
Extramedullary disease	
Yes	4 (12.1%)
No	29 (87.9%)
Prior allogeneic HCT	
Yes	13 (39.4%)
No	20 (60.6%)
Prior HMA	
Yes	20 (60.6%)
No	13 (39.4%)
Number of prior therapies for AML	
Median	2.0
Range	(1.0-8.0)
AML status	
Refractory	11 (33.3%)
Relapse 1	14 (42.4%)
Relapse 2	8 (24.2%)
HMA	
Decitabine	31 (93.9%)
Azacitadine	2 (6.1%)
Duration of first cycle of decitabine (days)	
5	15 (48.4%)
10	16 (51.6%)
Number of venetoclax cycles	
Median	2.0
Range	(1.0-10.0)

Haematologica. 2018 Sep; 103(9): e404–e407

Outcomes

Response	R/R AML (n = 33)
Overall response rate	**21 (64%)**
Complete response	**10 (30%)**
Complete response with incomplete count recovery	7 (21%)
Morphologic leukemia-free state	4 (12%)



Haematologica. 2018 Sep; 103(9): e404–e407

Teaching Points

- Vyxeos leads to improvement in survival outcomes compared to 7+3 in patients 60-75 years with secondary AML.
- Venetoclax + hypomethylating agent is an effective combination for AML patients ineligible for intensive chemotherapy or with relapsed disease.

THANK YOU