17th Multidisciplinary Management of Cancers: A Case-Based Approach

2017 Hematologic Malignancies Panel

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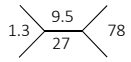
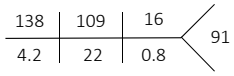
Case 1: 40 year-old male

- Followed for mild thrombocytopenia x 9 years (plts 120-140K)
- Develops recurrent skin infections and bronchitis; CBC shows new pancytopenia
- PMH limited to HTN, active with good PS.
- Exam – Fit, but tired-appearing gentleman. No splenomegaly. Otherwise unremarkable.



MCV 110
Diff:
Neutrophils 13% (ANC 169/mm^3)
Lymphocytes 86%
Monocytes 1%



EPO level 500 IU/L
TSH/B12/folate nl
Iron studies nl

Peripheral blood – no blasts or hemolysis

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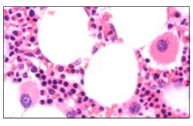
Case 1: Bone marrow biopsy

- HYPERCELLULAR MARROW WITH FEATURES OF MYELODYSPLASIA AND 5-6% BLASTS (SEE COMMENT)
  - 70% cellularity
  - 1+ fibrosis
  - Dysplasia evident in all three lineages
- Metaphase cytogenetics - 46,XY,del(7)(q11.2)[cp16]/45,X,Y,del(7)(q22q32)[4]/44-45,XY,-7[cp2]
  - Dominant monosomy 7 clone



Source: ASH image bank

What is the preferred initial treatment strategy for this patient?

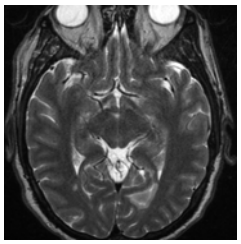
1. Trial of ESAs +/- G-CSF
2. Induction chemotherapy (7+3)
3. Hypomethylating agent
4. Lenalidomide
5. Myeloablative conditioning and allo-HSCT when donor source available

Case 1: High-risk MDS

- He has 2 living siblings in their 50s who are reportedly healthy; 1 daughter in her 20s with a reported immunodeficiency
- Mother died in her 50s of AML
- Given cytogenetics, ANC, and blast percentage, he is advised he has high risk MDS, referred to BMT and started on AZA
- Slight improvement in ANC/platelets after 2 cycles AZA
  - Baseline: WBC 1.3, ANC 169, Hb 9.5, platelet 78,000
  - Week 4: WBC 1.6, ANC 192, Hb 7.9, platelet 60,000
  - Week 8: WBC 1.3, ANC 325, Hb 7.8, platelet 57,000
  - Week 10: WBC 2.2, ANC 836, Hb 10.4, platelet 107,000
- Subsequently hospitalized with neutropenic fever; no source

Case 1: High-risk MDS

- While hospitalized develops acute right hemianopsia → MRI shows acute embolic stroke
- Closer examination finds mild arm swelling →found to have catheter associated upper extremity DVT



Case 1: High-risk MDS, CVA and PICC-associated DVT

- Extensive thrombophilia work up is negative
- Anticoagulated with unfractionated heparin
- Has a prolonged complicated hospital course with discovery of renal and splenic infarcts as well as worsening neutropenia. Evaluated for possible vasculitis. Repeat bone marrow biopsy to assess disease status recommended.

Sequencing which of the following genes would provide a potentially unifying diagnosis?

1. *KIT*
2. *FLT3*
3. *NPM1*
4. *GATA2*
5. *ASXL1*

Case 1: High-risk MDS, CVA and PICC associated DVT

Repeat bone marrow biopsy

```
bone marrow, aspirate
--   PERSISTENT MYELODYSPLASTIC SYNDROME, 2% BLASTS; HISTORY OF
MYELODYSPLASTIC SYNDROME WITH EXCESS BLASTS
--   HYPOCELLULAR MARROW WITH TRILINEAGE DYSPLASIA
     --   ADEQUATE IRON STORES WITH RING SIDEROBLASTS

BONE MARROW, FLOW CYTOMETRIC IMMUNOPHENOTYPING
--   ABNORMAL CD34+ BLAST POPULATION EXPRESSING CD13, CD56, CD117,
PARTIAL HLA-DR AND PARTIAL DIM CD5 (SEE FLOW INTERPRETATION)
```

Molecular analysis demonstrates heterozygous germline *GATA2* mutation (c.1186C>T, p.R396W) leading to GATA2 haploinsufficiency.

Case 1: Heritable *GATA2* mutations in familial MDS/AML

- GATA2 deficiency is an autosomal dominant disorder and has a broad phenotype with variable penetrance
- Immunodeficiency, MDS/AML, pulmonary disease, and vascular/lymphatic dysfunction
- Opportunistic infections including invasive fungal infections, nontuberculous mycobacterial infections
- Vasculitis and thromboembolism reported in the NIH series (25%)
- Clinical outcomes data for MDS/AML with GATA2 deficiency is sparse; allo-HSCT thought to be only curative option

Spinner et al, GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. *Blood* 2014

Germline mutations associated with familial MDS/AML

- *RUNX1*
- *CEBPA*
- *GATA2*
- *SRP72*
- *TERC*
- *TERT*
- *DDX41*
- *ATG2B and GSKIP*
- *ETV6*
- *ANKRD26*

Myeloid neoplasm classification
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or
Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.

Case 1: Outcome

- AZA on hold
- Being evaluated at Stanford as well as NIH for consideration of allo-HSCT
- Family members also being tested for *GATA2* (c.1186C>T, p.R396W) mutation

Case 1: Key Points

- While typically a sporadic disease, an increasing number of germline mutations have been associated with familial MDS/AML; a probing family history is critical
- One should determine whether the relevant gene exons carrying germline mutations are covered by the mutation panel(s) being ordered
- GATA2 deficiency can present with a broad clinical phenotype including lymphatic/vascular disorders, opportunistic infections (MonoMac) given monocytopenia, and MDS/AML
- If allo-HSCT is feasible, then siblings should be ruled out as carriers of the germline mutation

Case 2: 52 year-old male

- Presents with back pain and limb paresthesias
- Found on MRI to have spinal compression fractures and an epidural soft tissue mass causing cord compression
- Neurosurgery - thoracic laminectomy and resection of epidural mass
- Pathology demonstrates a plasma cell neoplasm

CD138 immunostain

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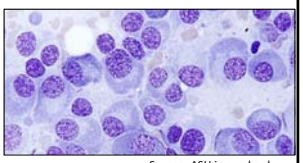
Source: ASH image bank

Case 2: Newly diagnosed multiple myeloma, male patient age 52

- Pertinent labs– hgb 12.6, calcium 9.0, creatinine 0.9, albumin 3.1, LDH 399 (ULN < 340), B2-M 4.2 mg/L
- **PET-CT: Small lytic lesions throughout spine**
- Monoclonal protein studies
  - FLC kappa 0.8
  - FLC lambda **61.8**
  - FLC ratio: 0.01
  - IgA **1800**
  - SPEP/IFE IgA lambda **3.3 g/dL**
  - Urine M-protein **1100 mg/24 hour**



Source: ASH image bank

- Bone marrow biopsy: **30%** lambda restricted plasma cells
- Cytogenetics/FISH reveal t(11;14) only; no del(17p)/t(4;14)/t(14;16)/t(14;20); no trisomies

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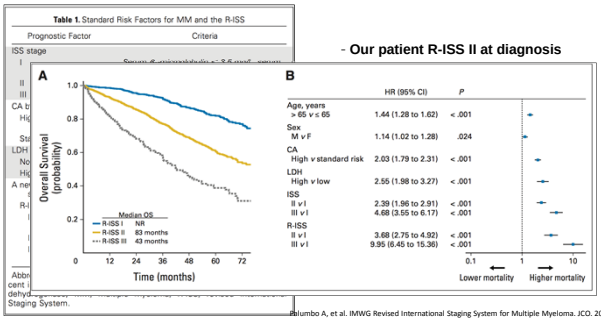
Based on the revised-IPSS model, how would you stage this patient at diagnosis?

1. R-ISS stage 0
2. R-ISS stage I
3. R-ISS sage II
4. R-ISS stage III

Case 2: Newly diagnosed multiple myeloma, male patient age 52



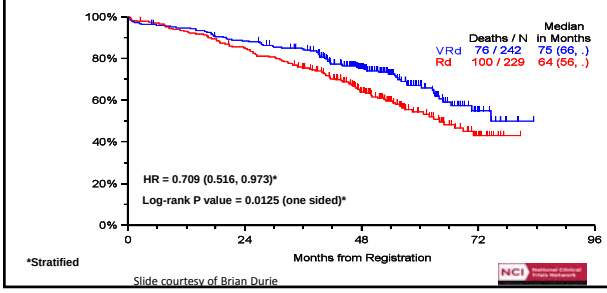
- Our patient R-ISS II at diagnosis

Palumbo A, et al. IMWG Revised International Staging System for Multiple Myeloma. JCO. 2015(33).

In addition to supportive care, what initial therapy would you recommend?

1. Lenalidomide-dexamethasone (Rd)
2. Lenalidomide-bortezomib-dexamethasone (RVd)
3. Carfilzomib-lenalidomide-dexamethasone (KRd)
4. Cyclophosphomide-bortezomib-dexamethasone (CyBord)
5. RVd + daratumumab

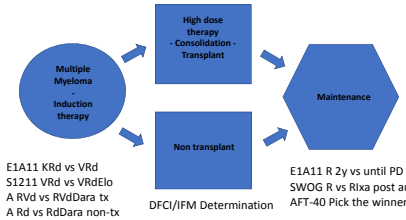
SWOG0777: OS By Assigned Treatment Arm



*Stratified

Slide courtesy of Brian Durie

Ongoing US Upfront Myeloma Trials



E1A11 KRd vs VRd
S1211 VRd vs VRdElo
A RVd vs RVdDara tx
A Rd vs RdDara non-tx

DFCI/IFM Determination

E1A11 R 2y vs until PD
SWOG R vs RIxa post auto (planned)
AFT-40 Pick the winner

Slide adapted from Phil McCarthy

Case 2: Newly diagnosed multiple myeloma, male patient age 52

- Upfront radiation to spinal canal
- Supportive care – antivirals, VTE prophylaxis, bisphosphonates
- 4 cycles of CyBorD→ Response: VGPR after 2 cycles, then plateau; develops neuropathy
- MEL200 and stem cell transplant→ Response: CR

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Which of the following regarding maintenance therapy post auto-HSCT is true?

1. Maintenance lenalidomide is associated with increased risk of secondary primary malignancies
1. Meta-analysis showed OS benefit for lenalidomide maintenance
1. Maintenance therapy increases depth of response
1. 1 and 2
1. All of the above are true

Case 2: Newly diagnosed multiple myeloma, male patient age 52

- Pt tests positive for minimal residual disease (MRD), but elects to be monitored without maintenance therapy
- Observed off therapy 12 months; gradually rising M-spike/sFLC
- Re-initiation of therapy is discussed, but patient needs to leave the country for important business deals

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Which of the following statements about MRD is not correct ?

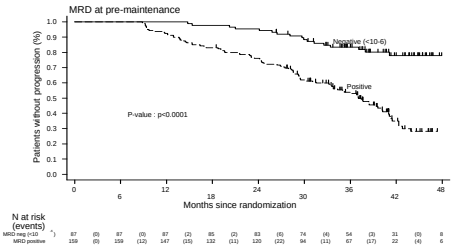
1. MRD status can be assessed by flow cytometry or next generation sequencing
1. There is no established international standard for MRD assessment
1. The PFS is shorter for patients who are MRD-positive after upfront ASCT compared to MRD-negative patients
1. The PFS is shorter for patients who are MRD-positive after salvage Len/dex/daratumumab compared to MRD-negative patients
1. Prolonged maintenance has been shown to overcome the negative prognostic effect of MRD-positivity

Slide 21

11 VTD is given to the patient, but it's not one of the choices (see prior slide)
Jason Gotlib, 1/22/2017

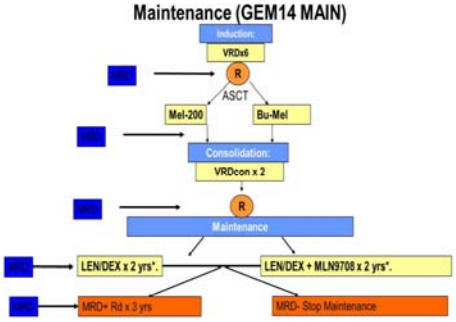
KG13 Changed to CyBorD
Kaufman, Gregory, 2/3/2017

MRD status predicts PFS post-ASCT in IFM 2009



Slide courtesy of Herve Avet-Loiseau

Maintenance (GEM14 MAIN)



* Patients with positive MRD will continue with LEN/DEX for 3 more years

Case 2: Treatment course (continued)

- 18 months s/p auto HSCT, presents with fatigue, diplopia and left eye proptosis
  - *Imaging: intraorbital/extraconal soft tissue masses with mass effect on the rectus muscles and globe*
  - *Biopsy of orbital lesion confirms plasma cell involvement*
- Bone marrow: 60% clonal plasma cells, FISH without additional cytogenetic abnormalities; M-spike 4.6 g/dl
- Imaging for other sites of possible extramedullary disease negative

→ **Radiation to the orbital plasmacytoma**

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Which of the following would be the least favored option for systemic therapy at this time?

1. Carfilzomib + lenalidomide + dex
2. Elotuzumab + dex
3. Daratumumab + lenalidomide + dex
4. Daratumumab + bortezomib + dex
5. Pomalidomide + bortezomib + dex

Lenalidomide-based salvage trials

	NRd vs Rd	KRd vs Rd	EloRd vs Rd	Dara Rd vs Rd
ORR	78%	87%	79%	93%
VGPR	48%	70%	33%	76%
CR	14%	32%	4%	43%
DOR, mo	20.5	28.6	20.7	NR
PFS benefit, mo	20.6 vs 14.7 **5.9 mo**	26.3 vs 17.6 **8.7 mo**	19.4 vs 14.9 **4.5 mo**	NR vs 18.4

Moreau P, et al NEJM 2015
Stewart AK, et al. NEJM 2015.
Lonial S, et al. NEJM 2015.
Dimopoulos, et al. NEJM 2016.

Case 2: Relapsed/Refractory MM

- Patient starts 4 cycles of carfilzomib, lenalidomide, dexamethasone
- Re-established disease control, achieving VGPR and continues on therapy

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Case 2: Key points

- Triplet novel agent induction has become the standard for fit patients; carfilzomib vs bortezomib and question of a 4th novel agent remain the subject of ongoing trials
- Position/sequencing of high-dose melphalan and auto-HSCT remains controversial, but still recommended upfront by many.
- Post-transplant maintenance prolongs progression-free survival
- Lenalidomide-based triplet salvage is superior to lenalidomide/dex

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Case 3: 35 year-old female

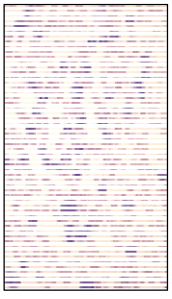
- 3 weeks of fatigue, sob/cough, no improvement with Z-pak
- Found to have leukocytosis
- No significant PMH; appears fit on exam
- spleen 6 cm below costal margin

78K 10.2 / 31 630K

138 | 105 | 10
4.3 | 24 | 1.0 116

Peripheral blood
- 40% band/segmented neutrophils
- 18% metamyelocytes
- 1% eosinophils
- 8% basophils
- 1% promyelocytes
- 16% myelocytes
- 4% blasts

Phosphorous 4.0 mg/dL
Uric acid 7.6 mg/dL
LDH 961 U/L
Coags/fibrinogen nl

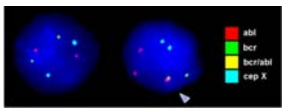


Source: ASH image bank

Case 3: 35 year old female

- Peripheral blood findings – rapid diagnostic FISH

FISH Analysis:
In situ hybridization (FISH*) was performed using the dual-fusion BCR/ABL1 probe (Abbott) which identifies the CML/ALL-associated Philadelphia translocation t(9;22). Two hundred interphase nuclei were scored for fusion signals consistent with rearrangement between the BCR and ABL1 genes. 165 (84%) of which were positive for double fusion signals.



- Diagnosis of CML, likely chronic phase; RT-PCR studies pending
  - Sokal and Hasford intermediate risk
- Diagnostic bone marrow recommended

The patient is hesitant about the necessity of a bone marrow biopsy and asks why it is recommended. You explain that:

1. 15 % of patients will be "upstaged" to accelerated or blast phase based on bone marrow findings.
1. Additional cytogenetic abnormalities may only be detected in the bone marrow.
1. Without an initial bone marrow, she would not be eligible for TKI discontinuation.
1. The bone marrow provides no more clinically useful information compared to PB FISH and/or RT-PCR

Case 3: 35 year-old female

- Bone marrow findings

DIAGNOSIS:
PERIPHERAL BLOOD, SMEAR
-- LEFT SHIFTED GRANULOCYTES WITH 3% CIRCULATING BLASTS
-- ABSOLUTE EOSINOPHILIA AND BASOPHILIA
-- HYPOCHROMIC NORMOCYTIC ANEMIA
-- THROMBOCYTOSIS

BONE MARROW, ASPIRATE AND BIOPSY
-- MORPHOLOGIC FINDINGS COMPATIBLE WITH CHRONIC MYELOGENOUS LEUKEMIA (SEE COMMENT)
-- 3% BLASTS BY MORPHOLOGY

BONE MARROW, ASPIRATE, FLOW CYTOMETRY IMMUNOPHENOTYPING
-- PARTIAL CD64 EXPRESSION ON GRANULOCYTES AND MONOCYTES
-- NO INCREASE IN BLASTS OR ABNORMAL BLAST POPULATION DETECTED
-- HETEROGENEOUS B, T, AND NK CELLS WITHOUT ABERRANT ANTIGEN EXPRESSION OR B CELL MONOCYTOPIA

  - Peripheral blood positive by RT-PCR for p210 *BCR-ABL1* transcript at diagnosis
- You recommend initial TKI therapy with dasatinib 100 mg daily.

Which of the following is true regarding initial TKI therapy in chronic phase CML in patients with intermediate Sokal/Hasford risk?

1. Imatinib, dasatinib, and nilotinib alll carry the same category 1 level recommendation in this setting.
1. Major molecular remission (MMR) rates are similar between imatinib, dasatinib, and nilotinib in patients with intermediate/high Sokal or Hasford risk scores
1. Fewer patients progressed to accelerated or blast phase in the DASISION (dasatinib) and ENESTnd (nilotinib) studies compared to imatinib
1. Five-year progression-free survival rates ultimately equalize between imatinib, dasatinib, and nilotinib.

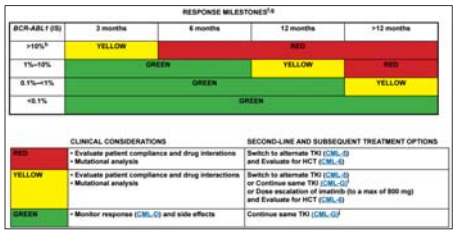
Case 3: 35 year old female, CP-CML initial TKI therapy with dasatinib

- Tolerates therapy well, mild fatigue, no dose reduction

Time from start of therapy	Hematologic response	Molecular response (IS)
3 months	Complete	8%
6 months	Complete	1.6%
9 months	Complete	0.6%
12 months	Complete	0.2%
18 months	Complete	0.1%
24 months	Complete	0.08%

Case 3: 35 year-old female, CP-CML initial TKI therapy with dasatinib

- 24 months, IS 0.08%, just below MMR threshold
- The patient expresses a desire to have a child and asks about getting pregnant.



Given the patient's molecular response status, disease and response to therapy in the context of her desire to have a pregnancy, you explain:

1. She should discontinue her TKI with close serial observation of IS values during pregnancy.
1. She should undergo *BCR-ABL1* mutation analysis to determine if another TKI could deepen her response prior to pregnancy.
1. She already meets criteria for TKI discontinuation so she can stop therapy.
1. She should continue dasatinib as teratogenic effects with TKIs have only been observed in animal studies

Case 3: 35 year-old female, CP-CML initial TKI therapy with dasatinib

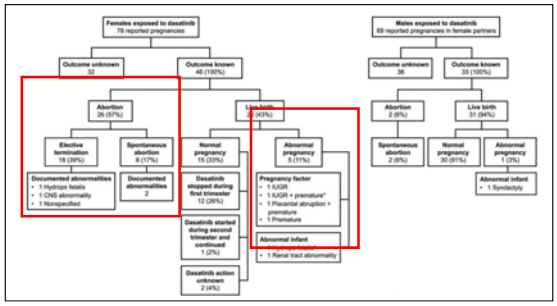
- Imatinib exposure in pregnancy

Table 1. Imatinib pregnancies

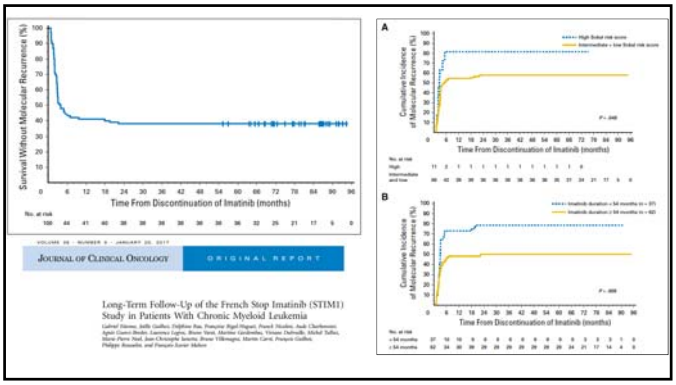
Pregnancy outcome	Timing of exposure in pregnancy by trimester, no. of patients					
	Before LMP	First trimester	After first trimester	Throughout pregnancy	Unknown	Subtotal
Spontaneous abortion	0	8	0	7	3	18
Elective termination						
Fetal defects	0	1	0	1*	1	3
Normal or unknown	0	20	0	5	7	32
Stillbirth with fetal defects	0	1	0	0	0	1
Live birth with congenital anomaly	0	6	0	0	2	8
Live birth without congenital anomaly	0	40†	1	18	4	63
Outcome unknown	1	27	3	7	17	55
Total	1	103	4	38	34	180

Pye, S., Cortes, J., Ault, P., Hatfield, A., Kantarjian, H., Pilot, R., Rosti, G. and Apperley, J. (2008). The effects of imatinib on pregnancy outcome. *Blood*, 111(12), pp.5505-5508.

Dasatinib exposure in pregnancy



Cortes, Jorge E. et al. "The Impact Of Dasatinib On Pregnancy Outcomes". *American Journal of Hematology* 90.12 (2015): 1111-1115.



Discontinuation Studies in CML-CP

Study	Rx before discontinuation	Response for discontinuation	Definition of relapse	TFR % (median f/U)
STIM1	IFN->I* for ≥3 yrs	MR4.5 for ≥2 yrs	Loss ofMMR or ≥1-log or increase in BCR-ABL	40 % (55mos)
STIM2	I for ≥3 yrs	MR4.5 for ≥2 yrs	Loss ofMMR or ≥1-log or increase in BCR-ABL	46 %at 2 yrs
ALLG CML8 (TWISTER)	I for ≥3 yrs	MR4.5 for ≥2 yrs	Loss of MMR or confirmed loss of MR4.5	42.7 % (42 mos)
A-STIM	I for ≥3 yrs	MR4.5 for ≥2 yrs	Loss of MMR	64 % (23 mos)
EUROSKI (in progress)	I, N*, D*	MR4 for ≥1 yr	Loss of MMR	61 % at 6 mos.
STOP 2G-TKI	N, D	CMR for median 29 mos	Loss of MMR	61.1 % (preliminary)

I=Imatinib, N=Nilotinib, D=Dasatinib

Mahon et al. Ann Hematol 2015,94:5187-93

Case 3: 35 year-old female, CP-CML initial TKI therapy with dasatinib

TKI discontinuation criteria per NCCN, Version 1.2017

- Chronic phase CML
- On TKI therapy for at least 3 years
- Prior evidence of quantifiable BCR-ABL1 transcript
- Stable molecular response MR4 (<0.01% IS) >2 years on at least 4 tests, 3 months apart
- No resistance to any TKI
- Monthly molecular monitoring for first 6 months
- Prompt resumption of TKI with loss of MMR

The above is an incomplete list; please see NCCN guidelines for full details

Case 3: 35 year old female, CP-CML initial TKI therapy with dasatinib

Resolution

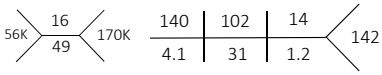
- Patient decided to discontinue dasatinib and pursue pregnancy
- Monitored q1-2 months off TKI
- IS slightly increased to 0.1-0.2 initially and then to 0.82% around the time of delivery
- Resumed dasatinib with re-achievement of pre—pregnancy IS values (<0.1%); avoids breastfeeding

Case 3: Key points

- Imatinib, dasatinib, and nilotinib all have evidence for frontline use in CP CML, though second-generation TKIs are favored in intermediate/high-risk patients
- Time-to and depth-of response targets are key to follow up
  - *Hematologic response*
  - *Cytogenetic complete response*
  - *Major molecular response*
- TKI interruption for pregnancy is recommended and assessed on a case by case basis with very close follow-up
- TKI discontinuation is recommended for only a minority of patients under strict criteria or on a trial basis

Case 4: 44 year old male

- Referred from primary care for lymphocytosis
- Asymptomatic
- No significant PMH; appears fit on exam
- No palpable lymph nodes, no hepatosplenomegaly

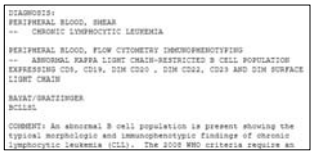


Peripheral blood
- 91% lymphocytes
- Smudge cells on peripheral smear

Source: ASH image bank

Case 4: 44 year old male

- Peripheral blood findings – flow cytometry



DIAGNOSIS:
PERIPHERAL BLOOD, SMEAR
-- CHRONIC LYMPHOCYTIC LEUKEMIA

PERIPHERAL BLOOD, FLOW CYTOMETRY IMMUNOPHENOTYPING
-- ABNORMAL KAPPA LIGHT CHAIN-RESTRICTED B CELL POPULATION EXPRESSING CD5, CD19, DIM CD20 , DIM CD22, CD23 AND DIM SURFACE LIGHT CHAIN

RAYAT/GRATZINGER
SCLL01

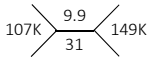
COMMENT: An abnormal B cell population is present showing the typical morphologic and immunophenotypic findings of chronic lymphocytic leukemia (CLL). The 2008 WHO criteria require an

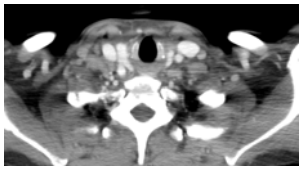
- FISH – de novo del17p13 deletion

Probe	Chrom. Target	No. cells	Result	Comment
D12Z3	trisomy 12	200	Negative	
ATM ATM	deletion at 11q23	200	Negative	
D13S319	del(13q14)	200	Negative	
P53 TP53	deletion at 17p13	200	Positive	11% nuclei w/ del(17p)

Case 4: 44 year old male

- Rai stage 0 CLL with del(17p) clone
  - 17p presence at diagnosis is rare ~7% of patients
- Patient recommended to have close observation
  - At 6 month follow up the patient noticed enlarging cervical lymph nodes as well as doubling of his ALC, new anemia and thrombocytopenia





Case 4: 44 year old male

- Adverse risk CLL with del(17p) clone
  - Initial treatment with ibrutinib 420 mg daily
  - At 1 month follow up, pt reports an increase in epistaxis and mild joint pains
  - At 6 months, pt has nearly normalized his ALC, normal hemoglobin, no lymphadenopathy, mild thrombocytopenia (platelet count 114,000)
  - Notes worsening symptoms including joint pains, mental "fog", moderate fatigue, bruising, and skin dryness
  - Patient given drug holiday and symptoms improved, but recurred with resumption of ibrutinib despite dose reduction

Among treatment-naïve CLL patients treated with ibrutinib, what is the most common reason for drug discontinuation?

1. Disease progression
2. Hypertension
3. Pneumonia
4. Atrial fibrillation
5. Prolonged MRD negativity

Case 4: 44 year old male

- 5 year follow up of ibrutinib, ASH 2016

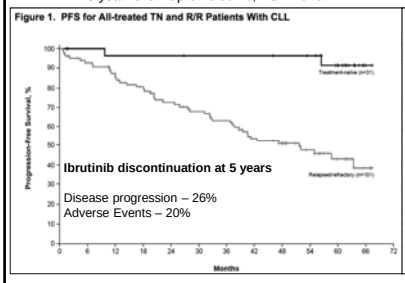


Table 3. Grade ≥3 AEs with ≥3% incidence

Adverse event*	TN ≥65 years (n = 31)	R/R (n = 101)	Total (n = 132)
Hypertension	7 (23)	20 (20)	27 (20)
Pneumonia	2 (6)	25 (25)	27 (20)
Neutropenia	1 (3)	18 (18)	19 (14)
Thrombocytopenia	1 (3)	10 (10)	11 (8)
Atrial fibrillation	2 (6)	6 (6)	8 (6)
Diarrhea	5 (16)	3 (3)	8 (6)
Fatigue	1 (3)	5 (5)	7 (5)
Sepsis	0	7 (7)	8 (5)
Cellulitis	0	5 (5)	5 (4)
Dehydration	0	5 (5)	5 (4)
Febrile neutropenia	0	5 (5)	5 (4)
Hyperglycemia	1 (3)	4 (4)	5 (4)
Hypokalemia	1 (3)	4 (4)	5 (4)
Sinusitis	0	5 (5)	5 (4)
Bacteremia	0	4 (4)	4 (3)
Decreased appetite	0	4 (4)	4 (3)
Decreased lymphocyte count	1 (3)	3 (3)	4 (3)
Increased lymphocyte count	0	4 (4)	4 (3)
Leukocytosis	0	4 (4)	4 (3)
Lymphocytosis	0	4 (4)	4 (3)
Syncope	1 (3)	3 (3)	4 (3)

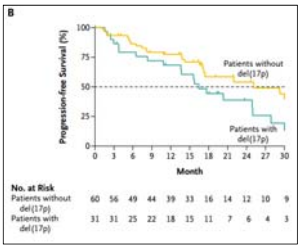
O'brien SM, Furman RR, Coutre SE, et al. Five-Year Experience with Single-Agent Ibrutinib in Patients with Previously Untreated and Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Blood 2016 128:233

What would you recommend for this patient (17p del, currently normal ALC) intolerant of ibrutinib?

1. FCR
2. Idelalisib + rituximab
3. Obinutuzumab
4. Venetoclax
5. Bone marrow transplantation
6. Observe until signs of relapse

Case 4: 44 year old male with CLL

- Pt initiated on venetoclax
- Small molecule oral bcl2 inhibitor approved by the FDA for relapsed/refractory CLL with del(17p)
- Good response rates (ORR 71%, CR 16%) and duration of response in del(17p) patients



Roberts A, Davids M, Pagel J et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. *New England Journal of Medicine*. 2016;374:311-322.

Case 4: 44 year old male with CLL

- **Venetoclax initiation**
  - Weekly oral escalation (20 mg daily → 50 mg qd → 100 mg qd → 200 mg qd →400 mg qd
- **Low tumor burden** (ALC<25k and lymph nodes < 5cm)
  - Oral hydration and allopurinol starting 2-3 days prior to start
- **Medium tumor burden** (ALC>25k or lymph nodes <10cm)
  - Oral hydration and allopurinol starting 2-3 days prior to start
- **High tumor burden** (ALC>25k AND any lymph node >5cm, or any lymph node >10cm)
  - Oral and IV hydration with inpatient monitoring, allopurinol starting 2-3 days prior to start

The patient completes venetoclax titration and is currently stable, no cytopenias, no lymphadenopathy. What would be your next step in management?

1. Bone marrow to confirm CR and MRD testing
2. HSCT referral now
3. FCR at progression→ HSCT
4. Idelalisib + rituximab at progression→ HSCT

Transplantation in high-risk CLL

Table 1. Prospective clinical trials with RIC HSCT in CLL: conditioning regimens and outcomes

	Dreger et al[25,26] (N = 90)		Sorror et al[24] (N = 82)		Brown et al[27] (N = 76)	
	%	Years	%	Years	%	Years
Conditioning regimen	Nonmyeloablative (fludarabine-cyclophosphamide with/without anti-thymocyte globulin)		Nonmyeloablative (fludarabine, low-dose total body irradiation)		Reduced-intensity (fludarabine-busulfan)	
Alternative donors†	59		37		63	
Relapse incidence	46	6	38	5	40	5
Progression-free survival	38	6	39	5	43	5
OS	58	6	50	5	63	5
5-y OS of patients with sensitive disease at HSCT	69‡		70§		79‖	
Follow-up, y						
Median	6.0		5		5.1	
Range	0.6-10.7		0.9-7.3			

Dreger P, et al. Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents?. *Blood*. 2014;124:3841-3849.

Transplantation in high-risk CLL

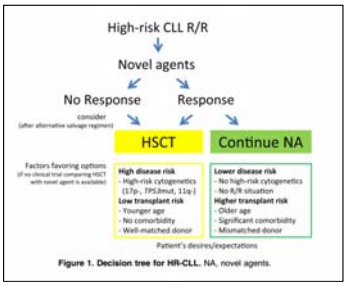


Figure 1. Decision tree for HR-CLL. NA, novel agents.

Dreger P, et al. Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents?. *Blood*. 2014;124:3841-3849..

Case 4: Key points

- Ibrutinib, while generally well tolerated, has a not insignificant discontinuation rate due to AEs; particularly in R/R pts
- Venetoclax is approved in relapsed CLL with del(17p)
- In young, high-risk CLL patients, transplantation remains a curative option

Case 5: 38 year-old female

- Referred for evaluation of thrombocytosis
- Thrombocytosis incidentally identified 14 months ago incidentally (plt 855K), only repeated by PCP 2 months ago (936K)
- PMH – migraines
- Medications - none
- Symptoms –chronic headache last 4 weeks (different from usual migraine), no bleeding, thrombosis, visual disturbance, pruritis, burning pain in hands or feet; menses unchanged/regular
- FH - unremarkable

Source: ASH image bank

Case 5: 38 year-old female

- Exam – appears fit, spleen and liver not palpable
  - Current CBC

14.5K	16.3	1072K
	49.2	

Differential:
Neutrophils: 72%
Lymphocytes: 13%
Monocytes: 10.3%
Eosinophils: 3%
Basophils: 1%

  - Prior CBC
    - 14 months ago

13	15.6	855K
	47	

No differential performed

- **Peripheral smear** – primarily mature neutrophilia; rare dacrocytes; no myeloid immaturity; occasional large and hypogranular platelets

Which of the following is the likely diagnosis?

1. Essential thrombocythemia (ET)
2. Polycythemia vera (PV)
3. Primary myelofibrosis (PMF)
4. Chronic myelomonocytic leukemia (CMML)
5. More information needed

Case 5: 38 year-old female

Pertinent labs
- **Ferritin 20**
- **EPO 2.8** (2.6 – 18.5 mIU/mL)
- ***JAK2* V617F mutation detected; allele burden 45%**
- VWF screen normal

- BM shows panmyelosis with an increase in loosely clustered, mature appearing megakaryocytes; MF-0 to patchy MF-1 fibrosis; cytogenetics: 46,XX [20]

- **Diagnosis of PV requires all 3 major criteria, or the first 2 major criteria and the minor criterion**

Table 4. WHO criteria for PV

WHO PV criteria
Major criteria
1. Hemoglobin >16.5 g/dL in men
Hemoglobin >16.0 g/dL in women
or,
Hematocrit >49% in men
Hematocrit >48% in women
or,
increased red cell mass (RCM)*
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor criterion
Subnormal serum erythropoietin level
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.

Case 5: 38 year-old female

- Major changes in the 2016 WHO revision to the diagnosis of polycythemia vera
  - Increased importance of the bone marrow biopsy (moved from minor to major criterion)
  - Lowering of the hemoglobin / hematocrit cutoffs for diagnosis; new cutoffs:
    - Men: hgb > 16.5 g/dL, hct>49% (down from Hb >18.5)
    - Women: hgb > 16.0 g/dL, hct>48% (down from Hb >16.5)

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.

What would you recommend as initial management for this patient?

1. Phlebotomy to maintain HCT ~45-50% and baby aspirin
2. IV iron and oral hydroxyurea
3. Phlebotomy to HCT<45% and baby aspirin
4. Ruxolitinib
5. Pegylated interferon-alpha

Case 5: 38 year-old female

- Optimal Hct in the management of PV?

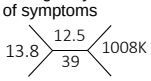
Cardiovascular Events and Intensity of Treatment in Polycythemia Vera Trial (Cyto-PV)

- 365 Patients – randomized to HCT target <45% or 45-50% with phlebotomy/hydroxyurea, or both
- Primary end point – composite death and major thrombotic event
- ITT analysis - <45% Hct group had 3-4 fold fewer events: 2.7% compared to 9.8% in the higher HCT group (p=0.007)

Marchioli *et al. New Engl J Med*. 2013;368:22-33.

Case 5: 38 year-old female

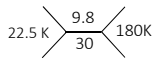
- Patient starts ASA 81 mg daily and undergoes 3 x 500 cc phlebotomies with improvement of symptoms
  - Current CBC



- Patient is counseled regarding the risk of progression to post PV-MF or MDS/AML
  - Lifetime risk of progression to post PV-myelofibrosis ~10-20%
  - 20 year risk of progression to MDS/AML ~5-10%

Case 5: Polycythemia vera, now age 50

- After 12 years of follow up and routine phlebotomy, the patient develops reduced phlebotomy requirement and eventually anemia; platelet count is now 'normal'
- Symptomatic splenomegaly 12 cm below the left costal margin
- Worsening fatigue, and weight loss of 15 lbs (>10% of body weight) over last 3 months with early satiety
- Bone marrow biopsy demonstrates MF-3 fibrosis and megakaryocytic hyperplasia with atypia
- Karyotype is normal



- 2% circulating blasts are noted in the peripheral blood

Differential:
Neutrophils: 60%
Lymphocytes: 20%
Metamyelocytes: 4.9%
Monocytes: 7.1%
Myelocytes: 3%
Promyelocytes: 1%

What is the DIPSS Plus prognostic score for this patient with post-PV MF, and what treatment would you recommend?

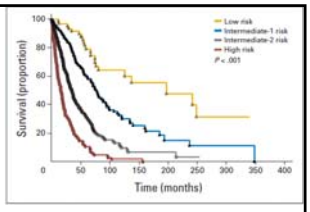
1. Intermediate-1; watchful waiting
2. Intermediate-1; pegylated interferon-alpha
3. Intermediate-2; hydroxyurea and referral for HSCT
4. Intermediate-2; ruxolitinib and referral for HSCT
5. High-risk; referral for immediate HSCT

- Age >65
- Hb < 10 g/dL
- WBC > 25,000/mm^3
- Constitutional symptoms
- Peripheral blood blasts ≥1%

IPSS

- RBC transfusion dependence
- Platelet count < 100,000/mm^3
- Unfavorable cytogenetics

DIPSS Plus



Primary Myelofibrosis Prognostic Scoring Systems

DIPSS Plus	# Adverse Points	Median Survival
Low risk	0	185 months (15.4 yrs)
Intermediate-1 risk	1	78 months (6.5 yrs)
Intermediate-2 risk	2-3	35 months (2.9 yrs)
High risk	4-6	16 months (1.3 yrs)

Gangat *et al*, *J Clin Oncol*, 2011

Case 5: Key points

- WHO 2016 guidelines have lower Hb/Hct requirements for the diagnosis of PV and now include cases once considered 'masked' PV or ET
- Hematocrit target <45% reduces the risk of thrombotic/cardiac complications in PV
- Ruxolitinib is better than best available therapy for symptomatic splenomegaly and MF-related symptoms
- Transplantation remains the only curative option for MF and should be considered in younger patients with intermediate to high risk MF
- The use of ruxolitinib to improve performance status and reduce splenomegaly before HSCT is increasingly used in practice, but is formally being studied in clinical trials

17th Multidisciplinary Management of Cancers: A Case-based Approach

Hematologic Malignancies Panel

Thank you!

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