


18th Multidisciplinary Management of Cancers: A Case-based Approach

Hematologic Malignancies Tumor Board 2018


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18th Multidisciplinary Management of Cancers: A Case-based Approach

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- Hyma Vempaty, MD – Department of Hematology/Oncology; TPMG
- Raj Krishnan, MD – Hematology/Oncology Fellow; UC Davis




18th Multidisciplinary Management of Cancers: A Case-based Approach

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	Lab	Value
WBC	145 K/mm ³	Potassium	3.4 mmol/L
Hgb	8 g/dL	Creatinine	0.61 mg/dL
Plt	77K/mm ³	LDH	1700 U/L
Blasts	54%	Uric Acid	3.4 mg/dL
ANC	16 K/mm ³	D-Dimer	900 ng/mL



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Case 1

- 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
- Patient had a central line placed and TTE shows a normal EF



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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

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- Patient is started on 7+3
- On Day 7, FLT3 mutational analysis returns positive for FLT3-ITD at 25%
 - Cytogenetics: 47 XX, +8[2]; 46 XX
- Midostaurin is started on Day 8 at 50 mg PO BID

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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

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- Her course was generally uncomplicated barring neutropenic fever and mucositis
- Next Generation Sequencing Myeloid Panel returned at this time 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

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What regimen should be chosen for re-induction?

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

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- 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%)

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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

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- 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

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What does the presence of MRD indicate in AML?

- A. It is currently unclear
- B. Higher relapse rate
- C. Increased need for HCT
- D. Worse Survival
- E. All of the above

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What is the role of allogeneic 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

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- Patient underwent matched related donor allogeneic HCT

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 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

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 1 Key Points

- The standard of care for AML is rapidly evolving
 - Four new FDA approvals in 2016
 - Midostaurin (FLT3 inhibitor)
 - Daunorubicin and cytarabine liposome
 - Gemtuzumab ozogamicin (anti-CD33 antibody-drug conjugate)
 - Enasidenib (IDH2 inhibitor)
- 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
- FLT3 inhibitors are being evaluated in the post-transplant setting

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END OF CASE 1

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 2

- 65 yo man with PMH including HTN presents with fatigue and noted enlarging bilateral cervical lymph nodes
- Examination reveals bilateral cervical and axillary LAP, the largest being 2 cm; splenomegaly noted; the remainder of his exam was unremarkable
- Pertinent labs were as follows:

Lab	Value
WBC	117 K/mm ³
Lymphocytes	90%
Hgb	8.2 g/dL
Hct	24%
Plt	77 K/mm ³
LDH	320 U/L

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 2

- PB Flow Cytometry was completed and revealed CD19/CD5+, CD10-, kappa restricted in 90% of the lymphocytes; they also are CD23+, CD20+ (dim)
- FISH, Zap70 and Ig Heavy Chain Mutational Analysis is sent
 - FISH: 13q deletion
 - Zap70: negative
 - IgVH: mutated
 - Cyclin D1: negative
- A diagnosis of Rai Stage IV CLL with del(13q) and IgVH mutated is confirmed



18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 2

Considering an ECOG = 0, what treatment should be offered to this patient?

- A. FCR
- B. CD20 antibody (Rituximab/Ofatumumab/Obinutuzumab) + Chlorambucil
- C. FCR-lite
- D. Ibrutinib
- E. Observation

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- Patient is started on FCR, to which he responds, but is complicated by profound and persistent pancytopenia
 - This leads to several admissions for febrile neutropenia, including ICU stays for sepsis
- After a prolonged recovery, the patient does well for 6 months
- Follow up at that time reveals a return of cervical LAP and a WBC of 122 K/mm³ along with anemia (Hgb 8.7 g/dL) and thrombocytopenia (Plt 62 K/mm³)

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What treatment should be offered at this time?

- A. Venetoclax + Rituximab
- B. Ibrutinib
- C. Rituxmab TIW
- D. Idelalisib + Rituximab
- E. Hospice

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Assuming a good response, what is the role of allogenic transplant?

- A. No role at all
- B. Proceed if a donor is found
- C. No role at this time
- D. Proceed if second line of therapy fails

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 2 Key Points

- FCR continues to have a role in the treatment of subsets of non-del(17p)/TP53 CLL patients
- Small molecular inhibitors are the mainstay of second line therapy in non-del(17p)/TP53 CLL patients
- Allogeneic hematopoietic cell transplant can be considered in fit patients with CLL refractory to small molecular inhibitors

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END OF CASE 2

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 3

- 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	Lab	Value
Creatinine	3.67 mg/dL	Kappa LC	4800 mg/dL
Ca	12.3 mg/dL	Lambda LC	6 mg/dL
Hgb	9.8 g/dL	K/L ratio	800
Albumin	3.9 g/dL	SPEP	No M-spike
B2M	5.7 mg/L	IFE	Negative
LDH	120 U/L	UIFE	Kappa LC

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

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Case 3

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

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Case 3

- 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

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Case 3

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

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Case 3

- 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

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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

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- Patient is started on maintenance Lenalidomide and Zometa
- 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

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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

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- 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

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- 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

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What treatment option should be offered next?

- Allo-HCT
- Clinical Trial with CAR T-cell therapy
- Continue KRd until progression
- Maintenance therapy
- Treatment Holiday

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- 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
- Twenty-five days after stem cell infusion, patient shows signs of engraftment however he starts to develop abdominal pain, nausea, vomiting and profuse diarrhea concerning for GI GvHD
- As infection was ruled out, he was started on steroids and underwent endoscopy
 - Biopsies showed Grade 3 GvHD of the duodenum and Grade 2 GvHD of the colon

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- The patient has no improvement in symptoms despite high-dose steroids in addition to his current immunosuppression regimen (MMF and Cyclosporine)
- Steroid dose was increased and Octreotide added with no improvement in diarrhea
- Due to the profuse volume of diarrhea (>2000 L/day), patient is deemed to have Grade IV GI GvHD
- IV nutrition is added to his regimen

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What further treatment options should be added for Grade IV GI GVHD?

- A. Photopheresis
- B. Etanercept
- C. Tocilizumab
- D. Budesonide
- E. Any/all of the above

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- Patient was given two doses of Etanercept without much improvement in symptoms
- ECP was started
- Budesonide was added next however patient unable to take consistently
- Tocilizumab was then administered for two doses (q3 weeks)
- Over the next 6 weeks, his symptoms improve, with Tocilizumab seeming to be the most effective for his diarrhea

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- Patient is discharged 5 months after stem cell infusion; his nutritional status is much improved
- Two years post-transplant, patient remains in remission with no evidence GVH and remains on monthly ECP

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 3 Key Points

- Induction with triplet novel agent therapy is the mainstay of frontline treatment for patients with multiple myeloma
- Autologous hematopoietic cell transplant followed by maintenance is recommended upfront for most transplant-eligible patients with a response to induction
- Salvage novel agent therapy, second auto-HCT and allo-HCT can be utilized in the setting of previously treatment multiple myeloma
- Severe acute gut GVHD is a devastating complication of allo-HCT and is associated with significant morbidity and mortality



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END OF CASE 3

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 4

- 72 yo woman with PMH including PE, HTN, CAD, TIA, HLD and Hypothyroidism presents in consultation for recently diagnosed MDS

- Diagnosis made/BMBx completed in Mexico after she was found to have pancytopenia

- Examination is largely unremarkable

- Pertinent labs were as follows:

Lab	Value
WBC	3.3 K/mm ³
ANC	1.2 K/mm ³
Hgb	13.3 g/dL
MCV	99
Pit	110

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 4

- Outside BMBx translated outside report:
 - "Hypercellular marrow for her age with heterogeneity. Megakaryocytes with hypobubulation and some with one nucleus and hypogranular. Erythroid lineage with asynchrony of nucleus/cytoplasm maturation, some with reticular chromatin and karyorrhexis. Myeloid lineage with hypogranular and megaloblastic with some hyposegmentation. 2% blasts. Consistent with MDS."
- Second opinion review of the BMBx slides at your institution, however, reveals no evidence of dysplasia

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- After further discussion, patient agrees to a repeat BMBx due to the discrepancies noted
 - Counts are stable at this time
- Repeat BMBx reveals a normocellular marrow (30%) with multilineage maturation and no excess blasts (2%); no evidence of dysplasia
 - Cytogenetics 46, XX
 - MDS FISH Normal
- Vitamin/Mineral deficiency workup negative

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Case 4

What is this patient's diagnosis?

A. MDS
B. ICUS
C. CCUS
D. CHIP
E. No diagnosis

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Case 4

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Proposed definitions of ICUS, CHIP, and CCUS





Proposed entity	Definition
Idiopathic cytopenia of undetermined significance (ICUS)	Single or multiple blood cytopenias that remain unexplained despite appropriate evaluation including marrow examination. If present, bicytopenia is not present (1.0% of cells per lineage). Patients with ICUS are not known to have a clonal disorder either because its clonal nature has been confirmed or because testing was performed but the assay did not reveal a clonal mutation.
Clonal hematopoiesis of indeterminate potential (CHIP)	Identification of a clonal mutation associated with hematopoiesis in an individual who does not yet meet WHO criteria for diagnosis of a hematologic neoplasm. Individuals with CHIP usually have normal complete blood counts, normal erythrocyte indices or mild red cell macrocytosis without anemia, or minimal and clinically insignificant cytopenias. If present, bicytopenia is not present (1.0% of cells per lineage).
Clonal cytopenia of undetermined significance (CCUS)	Patients who have clinically meaningful unexplained cytopenias (CCUS) and are also found to have a clonal mutation, yet meet no other WHO-defined criteria for MDS or another hematologic neoplasm.

WHO: World Health Organization; MDS: myelodysplastic syndrome.

Feature	ICUS	IDUS	CHIP	CCUS	MDS
Somatic mutation	-	-	± ^{1,2}	± ^{1,2}	± ¹
Clonal karyotypic abnormality	-	-	± ^{1,2}	± ^{1,2}	± ¹
Marrow dysplasia	-	±	-	-	±
Cytopenia	±	-	-	±	±

ICUS, idiopathic cytopenia of unknown significance;
IDUS, idiopathic dysplasia of unknown significance;
CHIP, clonal hematopoiesis of indeterminate potential;
CCUS, clonal cytopenia of unknown significance;
MDS, myelodysplastic syndromes

NCCN v1.2018 MDS










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Case 4

Next Generation Sequencing was not sent with the bone marrow. Should it be sent by peripheral blood at this time?





A. Yes, as it will change management
B. No, as it is costly and will not change management
C. Yes, but it will not change management
D. No, but it should be completed if a repeat BMBx is necessary

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Case 4

- NGS is not sent and patient is placed on active surveillance
- One year later, patient is noted to have worsening cytopenias
 - WBC 1.7 K/mm³, ANC 0.8 K/mm³, Hgb 9.5 g/dL, Plt 70
 - She does not require transfusions and has had no infectious or bleeding complications
- A repeat BMBx now shows trilineage dysplasia with 3% blasts, iron stains are positive with no increase in ring sideroblasts, no fibrosis, normal cytogenetics
 - Patient is diagnosed with MDS with Multilineage Dysplasia

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Case 4

2016 WHO CLASSIFICATION OF MDS^{1,2}

Subtype	Blood	Bone marrow
MDS with single lineage dysplasia (MDS-SLD) ³	Single or bicytopenia	Dysplasia in ≥15% of one cell line, <5% blasts
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors with ring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenias; ≥1 × 10 ⁹ /L monocytes	Dysplasia in ≥15% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenias; ≥2%–4% blasts, <1 × 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia, 8%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenias; 5%–19% blasts, <1 × 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ≥ Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ≥1% blasts on at least 2 occasions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts
Refractory cytopenia of childhood	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts

NCCN v1.2018 MDS



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INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)^{1,2}

Survival and AML evolution	Score value				
	0	0.5	1.0	1.5	2.0
Prognostic variable					
Marrow blasts (%) ³	<5	5-10	—	11-20	≥21-30
Karyotype ⁴	Good	Intermediate	Poor		
Cytopenia ⁵	0/1	2/3			

IPSS Risk category (% IPSS pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥2.5	0.4	0.2

For IPSS: Low/Intermediate-1 see MDS-3 and MDS-4
For IPSS: Intermediate-2/High see MDS-5

NCCN v1.2018 MDS

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R)⁶

Prognostic variable	Score value						
	0	0.5	1	1.5	2	3	4
Cytogenetic ⁷	Very good	—	Good	—	Intermediate	Poor	Very poor
Marrow blasts (%)	≤2	—	>2-≤5	—	5-10	>10	—
Hemoglobin	≥10	—	8-10	<8	—	—	—
Platelets	≥100	<50	—	—	—	—	—
ANC	≥3.0	<0.8	—	—	—	—	—

IPSS-R Risk category (% IPSS-R pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
VERY LOW (19)	51.5	8.8	Not reached
LOW (38)	>1.5-≤3.0	5.3	10.8
INT ⁸ (20)	>3.0-≤4.5	3	3.2
HIGH (13)	>4.5-≤6.0	1.6	1.4
VERY HIGH (10)	>6.0	0.8	0.7



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Case 4

What would be reasonable management at this time?

- A. Best Supportive Care
- B. Hospice
- C. Lenalidomide
- D. Erythropoietin Stimulating Agent
- E. Azacitidine



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Case 4 Key Points

- There are a spectrum of pre-malignant hematopoietic disorders, including ICUS, CHIP and CCUS, that can be associated with an increased risk of progression to a hematologic malignancy and increased risk of cardiovascular disease
- The testing for CHIP and CCUS and follow-up of patients identified with ICUS, CHIP and CCUS is not yet standardized
- The classification of MDS subtypes was recently updated in the 2016 WHO revision
- Prognostic scoring systems, such as IPSS-R, be used to predict disease natural history and inform the goals and choices of therapy for MDS



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END OF CASE 4

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 5

- 41 yo man with no significant PMH presents with 20 lb weight loss and fatigue as well as recurrent URIs
- Examination is significant for splenomegaly (15 cm below L costal margin)
- Labs reveal:

Lab	Value
WBC	242 K/mm ³
Hgb	11.7 g/dL
Plt	609 K/mm ³
Segs/Bands	57%
Basophils	5%
Blasts	5%

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- BMBx was completed showing a markedly hypercellular marrow with left shift and <3% blasts present
 - Cytogenetics showed t(9;22)
 - Quantitative peripheral Bcr-abl PCR p210 showed an IS of 90%
- Patient is diagnosed with chronic phase CML
- Sokal Score - high risk

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As patient was diagnosed in 2005, he was started on Imatinib. In 2018, what TKI should be offered first line?

- Imatinib
- Dasatinib
- Nilotinib
- Bosutinib
- Any of the above

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Case 5

- Patient has resolution of splenomegaly and achieved a Complete Hematologic Response after 2 months of treatment
- A BMBx completed at 6 months showed 1 of 20 cells with t(9;22) on cytogenetics and quantitative Bcr-abl showed a 2 log reduction
- At 12 months, BMBx was repeated and showed a Complete Cytogenetic Response and a quantitative Bcr-abl showed a 2.5 log reduction
- MMR was achieved by 15 months

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Case 5

- Patient has been in MMR since 2007 (limit of detection = MR^{4.0})
- Discontinuation is discussed with the patient, he is hesitant

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 5

Should Imatinib be discontinued?

- Yes, if he consents after discussion of risks and benefits
- No, because he is at significant risk of TKI discontinuation syndrome
- No, evidence is still unclear and should be completed only on trial
- No, as he has not proven to have achieved MR^{4.5} for greater than 2-3 years
- No, as he on a first generation TKI

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Case 5

If discontinued, how often should the patient be monitored with molecular monitoring?

- Monthly for the first year, 6 weeks for the second year and every 3 months thereafter
- Every 3 months indefinitely
- Once a month indefinitely
- Every 6 months
- Never, trend WBC and Plt count



18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 5 Key Points

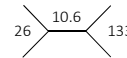
- With the recent approval of bosutinib, there are now four front-line options for the treatment of CP-CML
- Sokal and Hasford risk scores, along with side effect profiles and comorbidities, can help inform choice of initial TKI
- A subset of CP-CML patients can safely discontinue TKI therapy and remain disease free
- TKI withdrawal syndrome is a potential complication of TKI discontinuation

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END OF CASE 5

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 6

- 72 yo man with PMH including CAD, Hep C who presents in consultation for fatigue and night sweats
 - Hep C was treated with PEGylated-interferon- α -2a but had to discontinued due to depressive symptoms and cytopenias
- Examination was remarkable for splenomegaly
- After interferon was discontinued, WBC increased from 2.5 K/mm³ to 26 K/mm³

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 6

Auto differential: 89% neutrophils

Manual differential:





Neutrophils:	17%
Band forms:	27%
Lymphocytes:	11%
Metamyelocytes:	6%
Monocytes:	8%
Myelocytes:	15%
Promyelocytes:	14%
Blasts:	1%



18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 6

- Peripheral Smear reviewed and showed an increased number of left-shifted leukocytes with hypoblobation and pseudo Pelger-Huet morphology
- BMBx revealed a hypercellular marrow (95%) without increased blasts as well as mild dyserythropoiesis and dysmegakaryopoiesis primarily consisting of hypoblobated megakaryocytes with separate nuclear lobes; myeloid:erythroid ratio of 5:1
 - Cytogenetics show Trisomy 8 and no evidence of t(9;22)
 - Next Generation Sequencing showed *CSF3R* T618I (43% VAF) and *U2AF1* Q157T (48% VAF)










18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 6

What is this patient's diagnosis?

- Chronic Myeloid Leukemia
- Acute Myeloid Leukemia
- Chronic Myelomonocytic Leukemia
- Atypical Chronic Myeloid Leukemia
- Chronic Neutrophilic Leukemia










18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 6 – 2016 WHO Diagnostic Criteria

	CML	aCML	CNL	CMML
BLOOD				
WBC	nd	>13 x10 ⁹ /L	>25 x10 ⁹ /L	nd
Neutrophils and bands	nd	nd	>80%	nd
Immature granulocytes*	≥10%	≥10%	<10%	nd
Basophils	Present	Minimal or <2% of leukocytes	nd	Absent
Myeloblasts	Usually <2%	<20%	<1%	<20%
MARROW				
Granulocytic hyperplasia	Present	Present	Present	May or may not be present
Myeloblasts	Usually <5%	<20%	<5%	<20%
Granulocytic dysplasia	Minimal/absent	Prominent	Minimal/absent	May or may not be Present
Megakaryocytic dysplasia	Usually present	May or may not be present	Minimal/absent	May or may not be Present
OTHER				
Hepatosplenomegaly	nd	nd	Present	nd
BCR-ABL1 or variant transcripts	Present	Absent	Absent	Absent
PDGFRB, PDGFRB, or FGFR1 rearrangements	Absent	Absent	Absent	Absent
PN, PMF, or ET by WHO criteria	No	No	No	No
Monocytosis >1X10 ⁹ /L	Absent	Absent	Absent	Present





nd= not defined

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Case 6

- Patient first undergoes treatment for Hep C with Ledipasvir/Sofobuvir
- On presentation back to clinic, his spleen has increased in size and WBC has increased to 32.7 K/mm³
 - Hgb is now 9.5 g/dL and Plt count now 57 K/mm³
- Repeat BMBx shows increased blasts to 5%

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Case 6

What treatment option should be offered to the patient at this time?

- A. Allogeneic HCT
- B. Clinical Trial with Ruxolitinib
- C. Hydroxyurea
- D. Bcr-Abl TKI
- E. Hypomethylating Agent

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 6

Diagnosis	CSF3R Mutation Frequency
CNL	~80%
aCML	~5-10%
AML	~0.5% (TCGA)
ALL	Very rare

- CSF3R mutations are more frequent in CNL versus aCML
- There are two mutations of CSF3R which cause different signals
 - Truncation mutation = High SRC signaling
 - Point mutation (T618I – most common) = High JAK activation

Maxson et al, NEJM, 2013
Gotlib, Maxson, et al, Blood, 2013

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 6

- There is no established standard of care
 - Anecdotal evidence for therapy with treatment for MPN or MDS
- Allogeneic HCT is reasonable upfront in eligible patient with suitable donor
- Age, performance status, and use of myeloid mutation panels to identify actionable mutation(s) are useful factors in decision making

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 6

- Patient started Ruxolitinib on a clinical trial
- After 4 months, patient's splenomegaly resolved and symptoms improved
 - WBC decreased to 11.9 K/mm³ with Plt count of 130 K/mm³
- Patient however became transfusion dependent and two months later WBC and Plt worsened
- Repeat BMBx showed increased blasts (10%), increased monocytosis (40%), consistent with CMML-2
 - New CBL mutation found (67% VAF)



18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 6

What treatment should be considered at this time?

- A. Hypomethylating Agent
- B. Hydroxyurea
- C. Clinical Trial
- D. Low Dose Ara-C
- E. Allogeneic HCT after control of disease

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 6

- Patient started Decitabine and completed 3 cycles
 - BMBx after showed a reduction in blasts (3%) and stable CBC
- He then underwent a matched unrelated, reduced-intensity allogeneic transplant
- Post-transplant course was complicated by sepsis, renal failure requiring HD, acute and chronic GvHD and poor graft function
- Patient passed 13 months after transplant from severe sepsis

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 6 Key Points

- Establishing diagnosis of MPNs and MDS/MPNs can be challenging, and WHO 2016 criteria and molecular analyses should aid clinicians in the diagnostic process
- Due to the rarity of these diseases, standards of care are not well established or based on controlled studies
- There is a potential role for mutation-based targeted therapy in these diseases
- Prognosis is generally poor, although CMML can be risk stratified using PSS
- Hypomethylating agents and allo-HCT are often pursued if patients are eligible

18th Multidisciplinary Management of Cancers: A Case-based Approach

END OF CASE 6

18th Multidisciplinary Management of Cancers: A Case-based Approach

Bonus case (if time permits)

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 7

- 37 yo man with PMH including Type II DM and GERD who presents with 1 week of abdominal fullness, fever, productive cough, found to be pancytopenic on admission
- Examination revealed splenomegaly; no evidence of LAP and exam was otherwise unremarkable

- Initial labs reveal:

Lab	Value	Lab	Value
WBC	4.5 K/mm ³	Potassium	3.9 mmol/L
Hgb	10.1 g/dL	Creatinine	0.77 mg/dL
Plt	17K/mm ³	LDH	250 U/L
Blasts	50%	Uric Acid	3.7 mg/dL
ANC	0.19 K/mm ³	D-Dimer	1000 ng/mL

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 7

- BMBx is completed revealing a hypercellular marrow (90%) involved by 95% blasts
 - Flow Cytometry confirms Pre B-ALL (CD19/CD10/TDT+, CD20-)
 - Cytogenetics failed
 - ALL FISH reveals RUNX1/21q
 - Bcr-abl negative
 - Next Generation Sequencing pending

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 7

What treatment regimen should be started for this patient?

- Hyper-CVAD
- Clinical Trial
- Pediatric-inspired regimen (i.e. CALGB 10403, GRAALL-2003, etc.)
- Combination chemotherapy followed by Blinatumomab or Inotuzumab
- Combination chemotherapy followed by allogeneic HCT

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 7

- Patient was started on the pediatric-inspired regimen, CALGB 10403
 - LP did not reveal evidence of CNS disease (CNS-1)
- Next Generation Sequencing revealed:
 - IGH-CRLF2 rearrangement (Ph-like finding)
 - JAK2 D873N (subclonal), R683G and R683S
 - KRAS A146T, NRAS G13D (subclonal)
 - CDKN2A/B loss
 - IKZF1 K174fs*21
 - PTPN11 A72V, E69K (subclonal) and E76K (subclonal)

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 7

What is the significance of the findings from Next Generation Sequencing?

- No significance
- Unknown significance
- Poorer prognosis
- Prediction of response to therapy
- Change in therapy required

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 7

- Patient's course was complicated by biochemical TLS and DIC, neuropathy and mild transaminitis
- D29 BMbx was completed showing a hypocellular marrow (40%) with multilineage maturation and no excess blasts (2%)
 - Multiparameter MRD flow cytometry showed <0.01% lymphoblasts
- Given M1 marrow and <1% blasts after induction, the patient proceeded with Remission Consolidation (Course II) as per CALGB 10403

18th Multidisciplinary Management of Cancers: A Case-based Approach

Case 7

How should the MRD result be interpreted at D29?

- Patient is MRD positive
- Unknown significance of small population of blasts
- Patient is MRD negative
- Allogeneic HCT required at this time based on the MRD result
- Change in therapy required

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 7

- Patient continued on with Course II and Course III of CALGB 10403 without issues
- BMBx completed after Course III revealed a hypocellular marrow (30%) with decreased multilineage maturation and no excess blasts (2%)
 - MRD negative
- Patient had been evaluated by BMT during his first admission

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 7

What is the role of allogeneic HCT at this time?

- No role as he is in an MRD negative CR
- Proceed to transplant if a donor available
- Proceed to transplant considering Ph-like mutation at diagnosis
- No role, but consideration should be given to CAR T-Cell Therapy
- No role, but he should receive Bcr-Abl TKI

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 7

- Patient declined allo-HCT and is continued on CALGB 10403
- 4 months into maintenance, patient is found to have pancytopenia along with circulating blasts
- BMBx is repeated revealing a hypercellular marrow (85%) with increased blasts (15%)
 - Cytogenetics showed 46, XY with a normal ALL FISH
 - Next Generation Sequencing continues to show the IGH-CRLF2 and JAK2 clonal population

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 7

What is the next step in therapy for this patient?

- Allogeneic HCT now
- Blinatumomab followed by allogeneic HCT
- Inotuzumab followed by allogeneic HCT
- Combination chemotherapy + Bcr-Abl TKI
- CAR T-Cell Therapy

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 7

- Patient receives Blinatumomab, achieving a CRi and MRD negativity
 - His course was complicated by Grade 2 Cytokine Release Syndrome requiring only steroid administration
- Patient then proceeded to allogeneic HCT with a matched related donor
- On Day 100, BMBx is completed showing continued MRD negativity
 - Patient has only had issues with Grade 2 Skin GvHD

18th Multidisciplinary Management of Cancers: A Case-based ApproachCase 7 Key Points

- AYA patients (age 18-39) with Ph- ALL should be considered for initial treatment with a pediatric-inspired multiagent chemotherapy regimen
- Ph-like B-ALL is a high risk B-ALL subtype
- MRD status should be assessed in ALL and can be an indication for allo-HCT
- The care of R/R B-ALL is rapidly evolving with approvals in 2017 for:
 - Blinatumomab (CD19-CD3 BiTE)
 - Inotuzumab ozogamicin (anti-CD22 antibody-drug conjugate)
 - Tisagenlecleucel (CD19 CAR T-cell therapy)

18th Multidisciplinary Management of Cancers: A Case-based Approach

END OF CASE 7