Myelodysplastic Syndromes

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CAPhO Oncology Fundamentals Day 2018
Saturday, September 22
Objectives

• Describe the major clinical issues for patients with Myelodysplastic Syndrome (MDS).

• Explore the therapeutic options for treatment of MDS and for managing MDS symptoms.

• Discuss the therapeutic options for iron chelation therapy for patients at risk of complications from iron overload.
Myelodysplastic Syndromes (MDS)

• Heterogeneous group of myeloid clonal stem cell disorders

• Characterized by:
  • Hypercellular bone marrow
  • Blood cytopenias
  • Ineffective hematopoiesis
  • Predisposition to evolve to Acute Myeloid Leukemia (AML)
Question #1

• Which of the following best describes a typical patient presenting with MDS?

• A) 43 year old female with iron deficiency anemia with increasing cough
• B) 78 year old male with several comorbidities, increasing fatigue, and dyspnea
• C) 12 year old boy otherwise healthy with frequent infections
Myelodysplastic Syndromes (MDS)

• Typical patient characteristics:
  • Elderly (median age at diagnosis 76 years)
  • More common in men than in women
  • Given advanced age, often have multiple comorbidities, and difficulty tolerating intense therapy

• Incidence of MDS
  • General Population: 5 per 100,000 per year
  • Age 70-90: 30 per 100,000 per year
  • Age >80: 60 per 100,000 per year

Dipiro, Pharmacotherapy: A physiologic approach 2017 chapter e137
Myelodysplastic Syndromes (MDS)

• Major clinical problems are those associated with cytopenias
  • Anemia, neutropenia, thrombocytopenia
    • these translate to fatigue, transfusion support, infections and bleeding.

• Clinical course is variable ranging from an indolent and slow course to rapid development of AML
  • After progression to AML, disease tends to have lower response rate to standard therapy as compared to de novo AML

Dipiro, Pharmacotherapy: A physiologic approach 2017 chapter e137
NCCN Guidelines MDS Version 2.2018 accessed Aug 27, 2018
Etiology of MDS

• Exact cause is unknown, likely multifactorial

• Associations with exposure to agricultural chemicals and ionizing radiation (atomic bomb survivors in Japan)

• Risk of developing MDS in those:
  • with family history of hematologic malignancy
  • receiving chronic immune therapy to manage infectious and/or autoimmune diseases
  • prior radiation or chemotherapy (therapy related MDS)
Etiology of MDS

• “Therapy related MDS”
  • 10-15% of MDS cases
  • attributed to prior radiation or chemotherapy
  • most frequently reported chemotherapy are alkylating agents and topoisomerase II inhibitors
    • etoposide, anthracyclines, mitoxantrone
  • patients undergoing autologous HSCT
    • intense conditioning regimens with include high dose alkylating agents and/or etoposide
Pathophysiology of MDS

- Progressive bone marrow failure and ineffective hematopoiesis
  - Peripheral blood cytopenias (anemia, neutropenia, thrombocytopenia)
  - Terminally differentiated cells may have functional deficits

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Signs and Symptoms of MDS

• May be asymptomatic
  • cytopenias discovered on routine CBC

• Signs and Symptoms
  • Related to anemia
    • pallor, tachycardia
    • fatigue, lethargy, palpitations, dyspnea on exertion, exercise intolerance
  • Related to neutropenia
    • frequent infections
  • Related to thrombocytopenia
    • easy bruising/bleeding, petechiae, epistaxis

Dipiro, Pharmacotherapy: A physiologic approach 2017 chapter e137
Workup for Suspected MDS

• Laboratory Tests
  • CBC
  • Erythropoietin level
  • Iron studies: ferritin, iron, total iron binding capacity (TIBC)

• Bone Marrow Biopsy and Aspirate
  • Hematopathologist analysis
    • Morphologic examination, immunophenotyping and cytogenetics
Diagnosis of MDS

• Minimal Diagnostic Criteria:
  • Stable Cytopenia:
    • 6 months (2 months with specific karyotype or bilineage dysplasia)
    • Exclusion of another primary cause for dysplasia and/or cytopenias
  • At least one of the following:
    • Dysplasia (>10% in 1-3 major bone marrow lineages)
    • Blast count 5%-19%
      • Blasts of ≥ 20% is acute myeloid leukemia (AML)
    • A specific MDS associated karyotype
      • eg, del(5q), del(20q), +8, or del(7q)
Prognosis - MDS

Prognosis – MDS

• Considerations beyond IPSS-R
  • Genetic Mutations
    • Studies have identified > 40 recurrently mutated genes associated with MDS
    • 80% of MDS patients have at least 1 of these mutations
    • Some of the genes are associated with specific adverse features
      • Example T53 is associated with excess bone marrow blasts and severe thrombocytopenia

• Comorbidities
  • MDS patients are predominantly elderly
  • Approximately 50% of patients with newly diagnosed MDS present with one or more comorbidities
    • Most frequently cardiac disease and/or diabetes
## Selecting Treatment for MDS

<table>
<thead>
<tr>
<th>FACTORS TO CONSIDER</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Score / Risk Category (eg. IPSS-R)</td>
<td>Provides insight for risk of AML progression &amp; prognosis</td>
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<tr>
<td></td>
<td>For treatment, generally divide into two categories:</td>
</tr>
<tr>
<td></td>
<td>• Lower Risk: IPSS-R very low, low, intermediate</td>
</tr>
<tr>
<td></td>
<td>• Higher Risk: IPSS-R intermediate, high, very high</td>
</tr>
<tr>
<td>Comorbidities, Age, and Performance Status</td>
<td>Provides insight into ability to tolerate intensive treatment</td>
</tr>
<tr>
<td>Stability of blood counts over past few months</td>
<td>Provides insight into disease progression and potential</td>
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<tr>
<td></td>
<td>transformation to AML</td>
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<tr>
<td>Patient Preference</td>
<td>Shared decision making for choices of high or low</td>
</tr>
<tr>
<td></td>
<td>intensity therapy with/or supportive care</td>
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</tbody>
</table>
Treatment Overview – Higher Risk MDS

• Higher risk MDS:
  • very high, high, int* risk of R-IPSS

• GOAL – modify disease course, avoid progression to AML, extend survival

• OPTIONS:
  • Hypomethylating agents (HMA)
    • Azacitidine, (Health Canada Indication)
  • Low dose cytarabine
  • AML type chemotherapy (cytarabine + anthracycline)
    • Younger patients if high blast count, often a bridge to allogeneic SCT
  • Allogeneic SCT in eligible patients (small population)

Treatment Overview for Lower Risk MDS

• Lower risk MDS:
  • very low, low, int* risk on R-IPSS

• GOAL – ameliorate consequences of cytopenias and improve quality of life
  • focused on treatment of cytopenias
    • Anemia most common
    • Neutropenia and thrombocytopenia less common and rarely occur alone.
  • Transfusions of PRBC and/or platelets as indicated

Treatment Decisions for MDS

- MDS Clear Path
- http://www.mdsclearpath.org
Question #2

• Which of the following best describes lenalidomide for the treatment of MDS?

• A) It is indicated for thrombocytopenic patients with high risk MDS that is JAK2 positive
• B) It is indicated for low risk MDS that is not responsive to erythropoietin and filgrastim
• C) It is indicated for transfusion dependent patients with low risk MDS with deletion 5q cytogenetic abnormality
Lenalidomide

• Clinical Use:
  • Indicated for RBC transfusion dependent low or intermediate risk MDS with deletion 5q cytogenetic abnormality (del 5q)

• MOA:
  • Immunomodulator that is a structural and functional analogue of thalidomide
  • MOA not fully understood but multiple mechanisms identified including inhibition of the proliferation of hematopoietic tumour cells and increasing hemoglobin expression by erythroid cells

• Dose
  • Dose is 10 mg po once daily for 21/28 (with 7 day break) OR 28/28
Lenalidomide

• There is substantial evidence of causing fetal abnormalities (thalidomide analogue)

• Only available in Canada through a controlled distribution program called RevAid®
  • Prescribers, pharmacists, and patients must be registered with the program
  • Female patients of childbearing potential must use 2 simultaneous methods of contraception while taking lenalidomide
  • Male patients must use a latex condom during sexual contact with females of child bearing potential and must NOT donate sperm.
  • All patients must NOT donate blood
Lenalidomide

• Adverse Effects
  • Neutropenia (60%) or thrombocytopenia (60%)
    • dosage adjustment may be required if substantial myelosuppression
  • Thromboembolic events (DVT 5%, PE 3%)
    • Prophylactic anticoagulation (varying from ASA to warfarin to LMWH) may be appropriate
  • Secondary Malignancy
    • Acute leukemia (5%)
    • Solid tumours
  • Hypersensitivity reactions (1-5%)
    • Rash, pruritus, some reports of SJS or TEN
    • Pneumonitis like syndrome
  • Neurotoxicity
  • Somnolence
Azacitidine

• Clinical Use
  • Intermediate to high risk patients
  • Evidence shows decreased risk of leukemic transformation and lengthens median survival and hematologic response (as compared with supportive care alone)

• MOA:
  • Hypomethylating agent - Inhibits DNA methyltransferase leading to hypomethylation of DNA
Azacitidine

• Dose
  • 75mg/m²/day subcutaneously daily for 7 days every 28 days for at least 6 cycles (may be extended)
    • NOTE – 5 day regimens appear to have similar response rate but survival benefit only demonstrated with the 7 day regimen
  
  • Median number of cycles to first response is 3, with 90% of responses occurring prior to cycle 6
  
  • Best response typically occurs 3-4 cycles after initial response
Azacitidine

• Toxicities/Side Effects
  • Myelosuppression – neutropenia (nadir is 10-17 days), thrombocytopenia, anemia
  • Hepatotoxicity – especially in those with pre-existing hepatic impairment
  • Renal toxicity – can cause a rise in SCr or renal tubular acidosis (if serum bicarbonate decrease to <20 mEq/L, may need dosage adjustment)
  • Moderately emetogenic – patients may require an antinauseant prior to each dose
  • Tumour Lysis Syndrome – assess TLS risk prior to first dose/cycle (tumour burden)
  • Changes in bowel habits – diarrhea or constipation
Supportive Care - Cytopenias

• Neutropenia:
  • Consider G-CSF (or GM-CSF) for recurrent or resistant infections, role not well established
  • Use G-CSF in combination with erythropoietin/darbepoietin in some populations (example: ring sideroblasts ≥15% and EPO ≤ 500 mU/mL)

Supportive Care: Cytopenias

• Thrombocytopenia:
  • Platelet transfusions are recommended for thrombocytopenic bleeding or platelet count <10 X \(10^9\)/L
  • Antifibrinolytic agents (eg. Aminocaproic Acid or Tranexamic Acid) can be considered in refractory bleeding or severe thrombocytopenia

Supportive Care: Cytopenias

• Anemia:
  • If erythropoietin level is $\leq 500$ mU/mL and symptomatic anemia (and no del 5q), then treat with ESAs
    • High doses required
      • EPO 40,000U-60,000 U s/c once or twice weekly
      • Darbepoietin 150-300 mcg s/c every other week
    • Erythroid responses generally occur in 6-8 weeks
      • After response is achieved, can attempt to reduce the dose
    • Patients must be iron replete
    • If response not achieved, consider adding filgrastim
      • Synergistic erythropoietic activity due to enhanced survival of erythroid precursors.

Supportive Care: Cytopenias

• Anemia:
  • If del(5q) cytogenetic abnormality and transfusion dependence then treat underlying disease with lenalidomide

  • RBC transfusions are recommended for **symptomatic** anemia
    • Target Hg >80
    • Each unit of transfused red blood cells introduces 200-250 mg of elemental iron
    • Risk of Iron Overload (IO)
      • IO occurs after approximately 10-20 transfusions
      • Transferrin Saturation of > 55% in men or >50% in women supports diagnosis of Iron Overload

Clinical Consequences of Iron Overload (IO)

• Hepatic complications
  • IO associated liver cirrhosis

• Cardiac complications
  • cardiomyopathies

• Endocrine complications
  • diabetes
  • Hypothyroidism

• Iron Chelation Therapy (ICT)
  • may be indicated

Question 3

• Which of the following iron chelation therapies is most preferred by patients?

• A) Deferoxamine subcutaneous infusion
• B) Deferasirox dispersible tablets for oral suspension (Exjade®)
• C) Deferasirox film coated tablets (Jadenu®)
Deferoxamine

• MOA
  • Complexes with ferric ions, primarily in the vascular space, to form ferrioxamine which is renally eliminated

• Poor oral availability and short half life (t1/2 < 1 hour)

• Dose
  • Given subcutaneously or intravenously over 8-12 hours, 5-7 days/week
    • IV: 40 to 50 mg/kg/day (maximum: 60 mg/kg/day)
    • SC: 20 to 40 mg/kg/day
    • CrCl 10-50 mls/min – 25%-50% of normal dose

LexiComp Deferoxamine, Accessed Aug 13, 2018
Chalmers A. & Shammo J. Therapeutics and Clinical Risk Management 2016:12 201-208
Deferoxamine

• Side effects
  • Discomfort at injection site
  • Acute renal failure, increased serum creatinine
  • Urine Discoloration (pink / red / orange)
  • Hearing loss/tinnitus
  • Ocular disorders (elderly at higher risk)

• Drug Interactions with Ascorbic Acid (Vitamin C)
  • Increases risk of deferoxamine toxicities (left ventricular dysfunction is of particular concern)
  • Avoid ascorbic acid doses greater than 200 mg/day.

• Monitoring Parameters
  • SCr, auditory exams, ocular exams

LexiComp Deferoxamine, Accessed Aug 13, 2018
Chalmers A. & Shammo J. Therapeutics and Clinical Risk Management 2016:12 201-208
### Deferasirox tablets for ORAL SUSPENSION (Exjade®)

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>EXJADE® (deferasirox) tablets for oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Once-daily tablets for oral suspension</td>
</tr>
<tr>
<td></td>
<td>• Contains lactose and sodium lauryl sulfate (SLS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Thoroughly mix in liquid until fine suspension is obtained, and swallow*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resuspend any residue in a small amount of liquid</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Meal Considerations</th>
<th>Fasting for 30 minutes required</th>
</tr>
</thead>
</table>

- **Dispersible tablet for oral suspension**
- **Administration:**
  - Tablet mixed in water, orange juice, or apple juice until a fine suspension is obtained
  - Residual re-suspended and taken to get full dose
  - Take on an empty stomach

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Chalmers A. & Shammo J. Therapeutics and Clinical Risk Management 2016:12 201-208
Deferasirox Tablets for ORAL SUSPENSION (Exjade®)

• Dosing:
  • Initiation:
    • initiate at 20 mg/kg/day
    • titrate up by 5–10 mg/kg/day every 3-6 months based on iron store assessments to a max of 40 mg/kg/day
  • Dosage adjustment required for renal or hepatic impairment

• Issues:
  • 1/3 of patients find unpalatable
  • Adherence reported at approximately 70%
  • Abdominal pain, diarrhea, nausea, and vomiting
  • Contains lactose and sodium sulfate
    • Possible cause of gi side effects?
  • Rash

Chalmers A. & Shammo J. Therapeutics and Clinical Risk Management 2016:12 201-208
Deferasirox ORAL TABLET (Jadenu®)

- Same active ingredient as Exjade®
- New film coated tablet formulation
- Improved Tolerability??
  - Swallow whole (no suspending/tasting)
  - lacks lactose and sodium sulfate
  - Can take with a light meal if desired

Chalmers A. & Shammo J. Therapeutics and Clinical Risk Management 2016:12 201-208
Deferasirox ORAL TABLET (Jadenu®)

• Dose
  • Conversion from tablets for oral suspension (Exjade®)
    • Decrease dose by 30%
  • Initiation:
    • initiate at 14 mg/kg/day
    • titrate up by 3.5–7 mg/kg/day every 3-6 months based on iron store assessments to a max of 28 mg/kg/day
  • Dosage adjustment required for renal or hepatic impairment.

Chalmers A. Ther & Clin Risk Mngt 2016:12 201–208
Deferasirox - Tolerability of Formulations

• ECLIPSE study, 2017
  • Randomized open label phase II
  • 173 transfusion dependent thalassemia or MDS (IPSS very low to intermediate risk) randomized 1:1 to film coated (Jadenu®) vs disintegrating deferasirox tablets (Exjade®)
  • RESULTS (after 24 weeks of treatment):
    • Better adherence, palatability and patient satisfaction with film coated as compared with disintegrating tablet
    • Lower number of severe gi side effects with film coated tablet
    • Median serum ferritin reduction was 14% with film coated tablet vs 4% with disintegrating tablet

Deferasirox – Monitoring

• Renal function
  • SCr twice before starting and then monthly
  • Oral tablet (Jadenu®) - if CrCl rises > 33% from baseline for 1 week, decrease dose by 7mg/kg/day

• Hepatic function
  • LFTs baseline, twice weekly for 1 month, then monthly

• GI hemorrhage has been reported in advanced hematologic malignancy and thrombocytopenia
  • Contraindicated in plt < 50 X 10^9/L

• Audiology and ophthalmology exams
  • Neurosensory deafness and hearing impairment have been reported

Chalmers A. Ther & Clin Risk Mngt 2016:12 201-208
Summary

• The major clinical problems associated with MDS are related to cytopenias
• Consideration of patient age, life expectancy, comorbidities, patient symptoms and MDS disease factors are key in development of a treatment plan.
• Treatment options include agents that can modify the disease as well as supportive care for complications of cytopenias.
• The need for transfusions can lead to iron overload and associated organ toxicities.
• Iron chelation therapy may be an option, but challenges such as access, inconvenience, and tolerability to these agents may exist.
Questions?