Cardiac Amyloidosis: Overview of Disease State and Treatment

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Objectives For Pharmacists

- Describe the pathophysiology, symptomology, and diagnostic indicators of cardiac amyloidosis
- Recognize medications used for cardiac amyloidosis
- Explain relevant drug monitoring parameters while on therapy
- Identify the proper cardiac amyloidosis treatment modality given a patient case

Objectives For Pharmacy Technicians

- Describe cardiac amyloidosis
- List medications used for cardiac amyloidosis
- Recall how medications for cardiac amyloidosis help patients

Disclosures

I do not have any relevant financial relationships with any commercial interests to disclose

Pre-test

- What is the mechanism of action of patisiran?
- Which of the following would be the best option for the rhythm control management of atrial fibrillation in a patient with ATTR-CM?
- What is the preferred treatment regimen for patients with AL amyloidosis who will NOT undergo ASCT?
- Given a patient case which drug therapy would you like to start in this patient?

Cardiac Amyloidosis Overview

- Restrictive cardiomyopathy caused by buildup of amyloid fibrils in myocardium
- AL: Immunoglobulin light chain amyloidosis
  - Typically caused by abnormal proliferation of plasma cells
- ATTR: transthyretin amyloidosis
  - Misfolded transthyretin protein
    - Accumulates in myocardium (ATTR-CM) and neural tissue
  - Two types:
    - ATTRv
    - ATTRwt

ATTR-CM- amyloid transthyretin cardiomyopathy
ATTRv- amyloid transthyretin variant
ATTRwt- amyloid transthyretin wild type

Kittleson et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the AHA. *Circulation. 2020*; 142(1)

Indicators of Possible Cardiac Amyloidosis

- Symptomology:
  - Dyspnea
  - Fatigue
  - Edema
  - Moderate to severe left ventricular (LV) wall thickening (>14mm)

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Indicators of Possible Cardiac Amyloidosis

- Cardiac indicators:
  - Inability to tolerate antihypertensive or heart failure medications due to hypotension or orthostatic hypotension
  - Persistent low elevation of troponin
  - Unexplained atrioventricular (AV) block or prior pacemaker implantation
  - Mismatch between QRS voltage on electrocardiogram (EKG) and LV wall thickness on echocardiogram (Echo)
  - Family history of cardiomyopathy

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Indicators of Possible Cardiac Amyloidosis

- Non-cardiac indicators:
  - Neurological: paresthesia, weakness, orthostatic hypotension, gastroparesis, incontinence, urinary retention
  - Orthopedic: carpal tunnel, bicep tendon rupture, lumbar spinal stenosis
  - Family history of polyneuropathy

Diagnostic Testing

- Electrocardiogram (EKG)
  - Increased left ventricular wall thickness → evidence of left ventricular hypertrophy (LVH) or left bundle branch block on EKG
  - Conduction disturbances in sinus node and Purkinje fibers
  - Low QRS voltage
  - Psuedo-infarction patterns on EKG
  - Atrial fibrillation

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General Diagnostic Testing

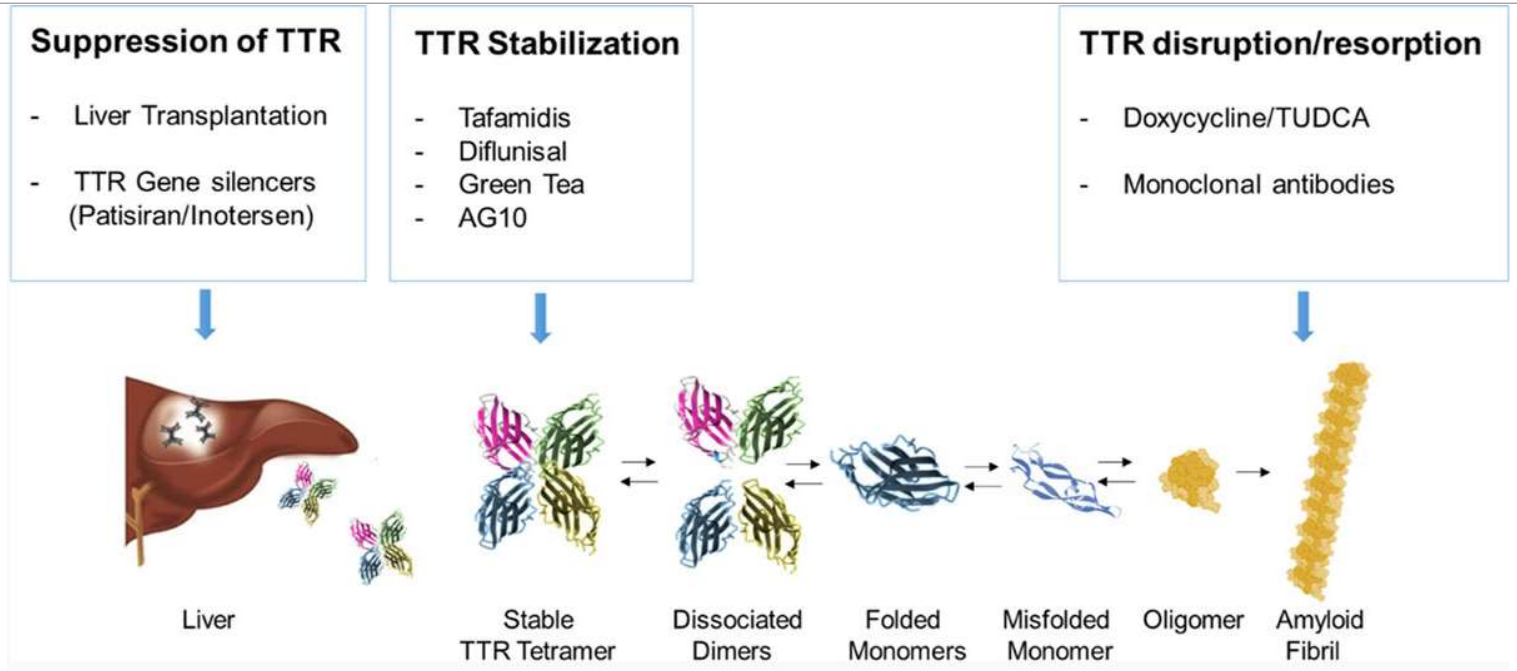
- Imaging:
  - Cardiac MRI: useful to differentiate constrictive pericarditis, myocarditis, or possible amyloidosis
  - Echo: thickened right ventricle, small LV cavity, impaired longitudinal strain
- Bone scintigraphy
  - Compares heart to rib uptake of technetium isotope in single photon emission computed tomography (SPECT)
  - Grade 2 to 3 (higher cardiac to rib intake of technetium) indicative of ATTR-CM

ATTR Amyloidosis

Diagnostic Testing for ATTRv

- Genotyping
  - Determines ATTRv vs ATTRwt
    - ATTRv warrants testing of family members
    - Val122Ile mutation generally more aggressive disease
  - Ancestry backgrounds for common genotypes
    - Val30Met: Portuguese, Swedish, and Japanese
    - Val122Ile: African American and African Caribbean
    - Thr60Ala: Irish

Mechanism of Treatment Strategies in ATTR



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TTR Silencers

Patisiran

- Small interfering (si, silencing) RNA → degrades TTR mRNA
- Intravenous, dose based on actual body weight (<100 kg, 0.3 mg/kg q3weeks, >/=100kg, 30 mg q3weeks)
- APOLLO trial:
  - Slower progression of amyloidosis related polyneuropathy
  - Subgroup analysis in patients with LV wall thickening showed reduced LV longitudinal strain, LV wall thickness, and NT-proBNP
- APOLLO-B: demonstrated efficacy of patisiran in cardiomyopathy
- Notable adverse drug reactions:
  - Infusion related reactions, reduced vitamin A levels

Patisiran. . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com
Kittleson et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the AHA. *Circulation. 2020;* 142(1)

Inotersen

- Single stranded antisense oligonucleotide → binds TTR mRNA → degradation
- Subcutaneous, 284 mg weekly with daily vitamin A supplementation
- NEURO-TTR trial:
  - Slower progression of amyloidosis related polyneuropathy
  - Stabilization of LV wall thickness, global systolic strain, and improved 6-minute walk test
- Notable adverse drug reactions:
  - REMS drug due to severe thrombocytopenia and glomuerulonephritis, vasculitis, decrease in vitamin A levels, hepatotoxicity, stroke and cervicocephalic arterial dissection

Inotersen. . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com
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TTR Stabilizers

Diflunisal

- Nonsteroidal anti-inflammatory drug that stabilized TTR in vitro
  - Dose: 250 mg by mouth twice daily
  - Must be taken with proton pump inhibitor
  - Associated with reduced neuropathies
  - Some evidence in ATTR-CM in small studies

Diflunisal. . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com
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Tafamidis

- Mechanism of action: binds thyroxine binding site of TTR
- 2 dosage forms: Vyndamax (61 mg PO qday) and **Vyndaqel (80 mg PO qday)**
- No adverse reactions listed in manufacturer's labeling
- ATTR-ACT trial:
  - All cause mortality (29.5 vs 42.9%; P<0.05)
  - Cardiovascular related hospitalization (0.48 vs 0.70 per year; P<0.05) at 30 months
  - Rate of decline in 6 minute walk distance (P<0.001)
  - Rate of decline in Kansas City Cardiomyopathy Questionnaire Overall Summary score (P<0.001)

Tafamidis. . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com
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Trial Drug: AG10

- Mechanism of action: binds to tetramer and mimics TTR T119M mutation → natural stabilization of TTR
  - Phase 2 trial indicated mortality and cardiovascular hospitalization were lower than placebo
  - Phase 3 trial in process

Potential TTR Disruption/Resorption

- Doxycycline and tauroursodeoxycholic acid
  - Potentially removes amyloid deposits
- Epigallocatechin-3-gallate
  - Green tea catechin
  - Inhibits amyloid formation in vitro
- PRX004
  - Monoclonal antibody
  - Currently under investigation

Audience Question

What is the mechanism of action of patisiran?

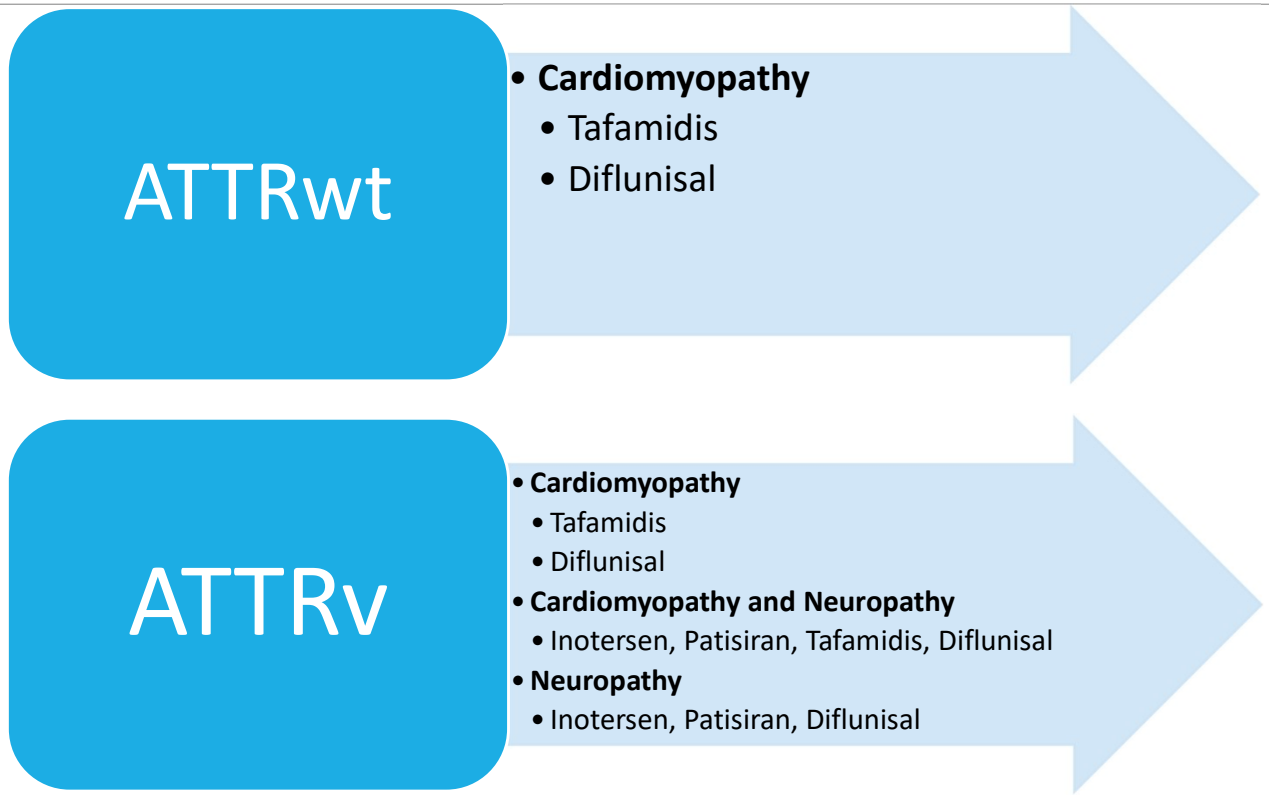
A. TTR Silencer

B. TTR Stabilizer

C. TTR Disrupter

D. None of the above

Which Disease Modifying Therapy to Use



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Heart Failure Management

- Low cardiac output state
  - Beta blockers and non-dihydropyridine (DHP) CCBs generally not tolerated
  - Diuresis useful in removing excess fluid volume
  - Aldosterone antagonists may be beneficial
  - Blood pressure reducing agents not recommended due to potentiating already existing hypotension

Heidenreich et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022; 145(18): 895-1032
Kittleson et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the AHA. *Circulation. 2020*; 142(1)

Advanced Heart Failure Therapies

- LV assist devices
  - Possible bridge to transplant
- Liver transplantation
  - Transplant removes ATTRv producing cells
  - ATTRwt protein is native → liver transplant ineffective
- Heart transplantation
  - Only definitive treatment for ATTR-CM
  - Preferred in ATTRwt
- Combined heart and liver transplantation
  - Preferred in ATTRv with neuropathy

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Arrhythmia Management

- Atrial and ventricular arrythmias common
- AHA HF guidelines recommend AC regardless of CHA_2DS_2-VASc score in patients with afib
  - Intracardiac thrombi occur in 1/3 of patients
- Rate control
  - Amiodarone- drug of choice
- Device implantation
  - Permanent pacemaker (PPM) or internal cardiac defibrillator (ICD) may be beneficial

AC- anticoagulation

Heidenreich et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022; 145(18): 895-1032
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Audience Question

Which of the following would be the best option for the rhythm control management of atrial fibrillation in a patient with ATTR-CM?

A. Digoxin

B. Amiodarone

C. Sotalol

D. Dofetilide

AL Cardiac Amyloidosis

Overview

- Deposition of protein derived from immunoglobulin light chains that misfold in organ tissue causing dysfunction
  - Produced by hematologic malignancies
- Can present in other organs besides the heart (50 – 70% of patients with cardiac involvement)
  - Kidney, nervous system, liver, muscles, skin
- Typical presentation of symptoms at age ≥ 40 years

Muchtar et al. Treatment of AL Amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Statement 2020 Update. Mayo Clinic Proceedings. 2020; 96(6)

Symptomology

- Proteinuria and nephrotic syndrome
- Neuropathy
- Heart failure symptoms
- Carpal tunnel syndrome
- AV block
- Loss of appetite
- Severe fatigue
- Unintentional weight loss
- Orthostatic hypotension

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Diagnostic Testing for AL Amyloidosis

- Biopsy of abdominal fat pad and bone marrow
  - If negative, biopsy affected organ
  - Determination of amyloid type done by chemical testing and staining
- Myeloma FISH panel
  - T(11;14)(q12;q32) most common type of mutation seen
  - Others include del(13q14) and gain of 1q21

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Muchtar et al. Treatment of AL Amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Statement 2020 Update. Mayo Clinic Proceedings. 2020; 96(6)

Diagnostic Testing for AL Amyloidosis

- M protein in urine or blood
  - Presence of monoclonal free light chain
    - Detection suggestive of monoclonal plasma cell proliferative disorder
  - Serum kappa/lambda free light chain ratio
    - Ratio <0.26 or >1.65 considered abnormal
  - Identified by immunofixation or serum protein electrophoresis

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Diagnostic Criteria

- Per Mayo Clinic and International Myeloma Working Group, all four must be present:
  - Presence of amyloid symptomology in affected organ
  - Positive amyloid staining by Congo red in tissue or detection of amyloid fibrils on electron microscopy
  - Presence of light chains by mass spectrometry or microscope
  - Monoclonal plasma cell proliferative disorder

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Staging

- Useful for estimating survival rate in stem cell transplantation vs non-transplantable
  - Mayo Stage 2004
    - NT-proBNP plus cardiac troponin T
  - Boston University Staging System
    - BNP plus cardiac troponin I
  - **Revised Mayo Stage 2012**
    - NT-proBNP, cardiac troponin T, and serum free light chains
- Changes in NT-proBNP associated with disease progression and response to treatment
  - Decrease in >30% associated with better prognosis

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AL Specific Treatment

- Heart failure, arrhythmias, anticoagulation managed similarly to ATTR
- Transplant
  - Heart transplant potentially an option in select cases
  - Kidney transplant feasible in end stage renal disease (ESRD)
  - Liver transplant not recommended
- Autologous hematopoietic cell transplantation (HCT)
- Chemotherapy
  - HCT vs non-HCT determines regimen choice

Autologous Hematopoietic Cell Transplantation (HCT)

- General criteria for ASCT
  - Age ≤ 70
  - Troponin T <0.06 ng/mL
  - Systolic blood pressure (SBP) ≥ 90 mmHg
  - Creatinine clearance ≥ 30 mL/min unless on dialysis
  - ECOG performance status ≤ 2
  - New York Heart Association (NYHA) functional status class I or II
  - No more than two organs involved
  - Not on home oxygen

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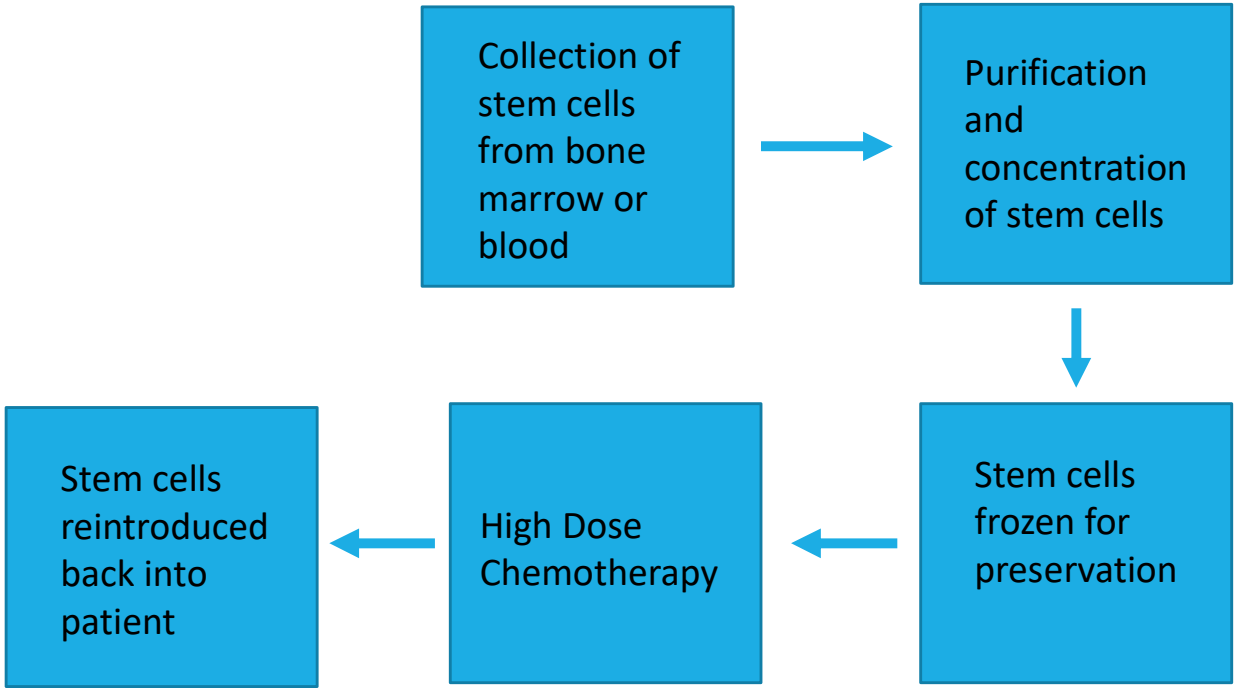
Autologous Hematopoietic Cell Transplantation (HCT) Process



Transplantable Patients

- Induction therapy followed by high dose melphalan → autologous HCT
  - Induction therapy:
    - Daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (dara-CyBorD) preferred
  - Avoid regimens with immunomodulatory derivatives (lenalidomide, thalidomide)

Non-Transplantable Patients

- Dara-CyBorD preferred regimen
  - Andromeda trial demonstrated better response compared to CyBorD alone
    - Hematologic complete response 53 vs 18% (relative risk ratio, 2.9; 95% CI 2.1 to 4.1)
    - Cardiac response 42 vs 22%
    - Death (hazard ratio 0.58; 95% CI 0.36-0.93)

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Daratumumab

- MOA: monoclonal antibody against CD38 → inhibits the growth of CD38 expressing tumor cells by causing apoptosis
- Intravenous and subcutaneous formulations
- Requires premedication with corticosteroid, acetaminophen, and antihistamine 1 to 3 hours prior to administration
- ADRs: **bone marrow suppression, HBV reactivation**, fatigue, headache, arthralgia, limb pain, infusion reactions, fever

ADRs- adverse drug reactions
MOA- mechanism of action

Daratumumab . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com

Cyclophosphamide

- MOA: alkylating agent preventing cell division by cross linking DNA strands and preventing cellular DNA formation
- Dose adjustment for impaired renal function
  - Considerations for dose adjustments based on hepatic function (cyclophosphamide is a prodrug)
- ADRs: bone marrow suppression (BMS), cardiotoxicity, hemorrhagic cystitis, hepatotoxicity, pulmonary toxicity, secondary primary malignancy

ADRs- adverse drug reactions
MOA- mechanism of action

Cyclophosphamide . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com

Bortezomib

- MOA: inhibits chymotrypsin-like activity at 26S proteasome → cell cycle arrest → apoptosis
  - Proteasomes regulate protein homeostasis in cell
- Dose adjustment for impaired hepatic function
- Dosing adjusted if toxicity occurs based on severity of ADR and indication of use
- ADRs: BMS, cardiotoxicity, hepatoxicity, neuropathy, posterior reversible leukoencephalopathy syndrome, progressive multifocal leukoencephalopathy, edema
- Cannot be given intrathecal

ADRs- adverse drug reactions
MOA- mechanism of action

Bortezomib . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com

Melphalan

- MOA: alkylating agent → inhibits DNA and RNA synthesis via formation of carbonium ions and cross linking of nucleotides
- Dosing for autologous HCT: 200 mg/m2
- Considerations for dose reduction in renal dysfunction
- Formulations/products not equivalent
- Moderate to high emetic potential
- ADRs: BMS, GI toxicity, mucositis, hepatotoxicity, pulmonary toxicity, secondary malignancy, electrolyte abnormalities, edema

ADRs- adverse drug reactions
MOA- mechanism of action

Melphalan . Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, Il. Available at: http:online.lexi.com

Alternate Regimens

- CyBorD
  - Decreased rates of lymphopenia, upper respiratory tract infections (URTI), neuropathy compared to addition of daratumumab
  - Hematologic response seen in 60 to 65% of patients
  - Cardiac response seen in 17 to 33% of patients
- Bortezomib, melphalan, dexamethasone (BMD)
- Melphalan and dexamethasone

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Determining Response to Initial Therapy

- Different systemic therapy is indicated in:
  - Hematologic or organ progression of disease
  - <50% reduction in difference between involved free light chain (FLC) and uninvolved free light chain (dFLC) levels after two cycles of chemo
  - dFLC >/= 40 mg/L after four to six cycles of chemo or on day 100 after transplant

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Refractory Disease

- Daratumumab-based regimens
  - Phase II trial with 40 patients with median of three prior therapies
    - Very good partial response seen in 48% of patients
    - Median time to response of one week
    - Median progression free survival of 25 months

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Refractory Disease

- Proteasome inhibitor regimens
  - Bortezomib
  - Ixazomib (oral)
    - TOURMALINE-AL1 trial
      - 168 patients with relapsed or refractory disease
      - Ixazomib plus dexamethasone vs non-proteasome inhibitor based regimen
      - 50% of patients had hematologic response
      - Longer treatment duration (median 11.7 to 5.0 months) and median time to decline in organ function or mortality (35 vs 26 months)
    - Notable ADRs: diarrhea, rash, cardiac arrhythmias, nausea

ADRs- adverse drug reactions
MOA- mechanism of action

Refractory Disease

- Immunomodulatory derivatives
  - Lenalidomide with low dose dexamethasone +/- cyclophosphamide
    - Increased risk of thromboembolic so must be on VTE prophylaxis
    - Low incidence of neuropathy
  - Pomalidomide plus dexamethasone
  - Thalidomide plus low dose dexamethasone +/- cyclophosphamide
    - Increased risk thromboembolism so requires VTE prophylaxis
    - ADRs: bradycardia, worsening heart failure, neuropathy

Refractory Disease

- Bendamustine plus dexamethasone
  - Reserved for patients that have failed multiple other regimens
  - ADRs: myelosuppression, fatigue, nausea, vomiting

Audience Question

What is the preferred treatment regimen for patients with AL amyloidosis who will NOT undergo ASCT?

A. CyBorD

B. Melphalan and dexamethasone

C. Dara-CyBorD

D. lenalidomide and dexamethasone

Prognosis

- Determined by extent of organ involvement
- 30 – 45% mortality within 6 to 12 months
- Advanced stage has median survival as short as 4 to 6 months
- Patients with limited organ involvement can survive for several years
- Concomitant myeloma or Waldenstrom macroglobulinemia worsen prognosis

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Patient Case

Patient KS

- 70 year old male of Caribbean decent
- Primary problem: new onset heart failure symptoms, neurologically intact
- Other past medical history: afib with left atrial appendage thrombus, hypertension
- Imaging: echo demonstrating LVEF 25% with small LV cavity and longitudinal strain
- Right heart cath with biopsy showing:
  - Pathology consistent with ATTR-CM
  - V122I gene
- Relevant medications prior to admission:
  - Apixaban
  - Lisinopril
  - Hydralazine

Patient KS

- Which medication would you like to start in KS?
  - A. Dara-CyBorD
  - B. Patisiran
  - C. Dexamethasone
  - D. Tafamidis

Applications to Practice

- Tafamidis remains the current mainstay of medical management for patients with ATTR-CM
- Heart +/- liver transplant currently only curative options for advanced disease in ATTR-CM
- Dara-CyBorD +/- autologous HCT provides the most efficacious response in the treatment of AL amyloidosis
- New data and treatments on the horizon in both AL and ATTR amyloidosis

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