NEET SS 2024 DrNB CLINICAL HAEMATOLOGY Paper3 Question Paper with Solution

Time Allowed :3 Hours	**Maximum Marks :**100	**Total Questions :**10

General Instructions

Read the following instructions very carefully and strictly follow them:

1. The test is of 3 hours duration.
2. The question paper consists of 10 questions. The maximum marks are 100.
3. Each Question is of 10 marks.

1. a) Discuss the diagnostic criteria for Waldenström's macroglobulinemia (WM).

Solution:

Step 1: Understanding Waldenström's Macroglobulinemia.
Waldenström's macroglobulinemia (WM) is a rare, indolent B-cell lymphoma characterized by the presence of monoclonal IgM antibodies produced by malignant lymphoplasmacytic cells. WM typically affects older adults and is associated with symptoms like hyperviscosity, neurological symptoms, anemia, and organ infiltration. The disease is diagnosed by a combination of clinical, laboratory, and histological criteria.

Step 2: Diagnostic Criteria.
The diagnostic criteria for WM include: 1. **Lymphoplasmacytic infiltration in the bone marrow:** The presence of malignant lymphoplasmacytic cells infiltrating the bone marrow is a hallmark of WM. A bone marrow biopsy is performed to confirm this infiltration.
2. **Monoclonal IgM paraprotein:** A monoclonal spike in serum protein electrophoresis (SPEP) or immunofixation electrophoresis (IFE) is observed, indicating the presence of IgM paraprotein. Elevated serum IgM levels are seen in the majority of WM patients.
3. **Presence of symptoms or organ involvement:** Symptoms such as fatigue, weight loss, peripheral neuropathy, or organomegaly (liver or spleen) may be present. Hyperviscosity syndrome is common in WM and is a key diagnostic feature. A visual disturbance or neurological deficits might indicate hyperviscosity.

Step 3: Genetic and Molecular Testing.
Genetic mutations such as MYD88 L265P are found in the majority of WM patients and serve as a diagnostic marker. CXCR4 mutations, which are seen in a smaller proportion of patients, are associated with resistance to certain therapies. These mutations can be detected through next-generation sequencing (NGS) or polymerase chain reaction (PCR).

Quick Tip

The key diagnostic elements of WM are the presence of monoclonal IgM, bone marrow infiltration by lymphoplasmacytic cells, and hyperviscosity symptoms. Genetic testing for MYD88 and CXCR4 mutations aids in diagnosis.

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1. b) Discuss the prognostic factors & prognostic system in WM.

Solution:

Step 1: Key Prognostic Factors in WM.
The prognosis of Waldenström's macroglobulinemia is influenced by various factors, including clinical, laboratory, and genetic parameters. Some of the most important prognostic factors are: 1. **Age:** Older age is generally associated with a worse prognosis, as it may indicate a more aggressive disease course or decreased ability to tolerate treatment.
2. **Serum IgM levels:** High levels of IgM are typically associated with a greater tumor burden, hyperviscosity, and worse outcomes. Patients with high IgM levels may also have a higher risk of developing complications.
3. **Performance status:** Poor performance status, often measured by the ECOG (Eastern Cooperative Oncology Group) scale, is an indicator of overall health and reflects the ability to undergo aggressive treatments.
4. **Genetic mutations:** MYD88 L265P mutation is associated with better prognosis and favorable response to treatments such as ibrutinib. CXCR4 mutations are linked to a poor prognosis and resistance to certain therapies, making them a critical factor in treatment decision-making.

Step 2: Prognostic Systems in WM.
The International Staging System (ISS) for WM is commonly used to classify patients based on prognostic factors. It evaluates factors such as serum beta-2 microglobulin, hemoglobin levels, and albumin levels to stratify patients into different risk categories: 1. **Stage 1:** Low-risk, with favorable levels of beta-2 microglobulin, hemoglobin, and albumin.
2. **Stage 2:** Intermediate-risk, with moderate levels of beta-2 microglobulin.
3. **Stage 3:** High-risk, with elevated beta-2 microglobulin and poor performance status.

Step 3: Further Genetic Considerations.
Genetic testing has become increasingly important in determining prognosis. MYD88 mutation-positive patients generally have a better prognosis and respond well to targeted therapies. In contrast, CXCR4 mutations are associated with resistance to ibrutinib and other therapies, leading to a poorer prognosis.

Quick Tip

The ISS staging system plays a key role in prognostication in WM. Genetic testing for MYD88 and CXCR4 mutations helps tailor therapy and predict outcomes.

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1. c) Discuss the treatment response & outcomes based on these prognostic factors.

Solution:

Step 1: Treatment Response Based on Prognostic Factors.
The treatment response in WM varies according to the patient's risk profile, which is influenced by clinical factors and genetic mutations. The following considerations are important: 1. **High IgM levels:** Patients with high IgM levels may require more aggressive treatment regimens, including chemotherapy or chemo-immunotherapy, to reduce tumor burden and manage hyperviscosity.
2. **MYD88 mutations:** Patients with the MYD88 L265P mutation generally have a good response to Bruton's tyrosine kinase inhibitors (BTK inhibitors) like ibrutinib, which help control the disease.
3. **CXCR4 mutations:** These patients are often resistant to BTK inhibitors and may require alternative therapies, including chemotherapy or monoclonal antibodies.

Step 2: Treatment Outcomes.
The treatment outcomes in WM are influenced by several factors, including: 1. **Low-risk patients:** Those with low-risk features, such as a favorable ISS stage and MYD88 mutation, often experience prolonged remission with minimal therapy, such as rituximab.
2. **High-risk patients:** Patients with high-risk features, including poor performance status, high IgM levels, and CXCR4 mutations, may have a more challenging course, requiring more intensive and potentially less effective treatments.

Step 3: Overall Management Strategy.
A personalized treatment approach is essential for WM. Genetic testing and staging systems guide treatment selection, ensuring the best possible outcomes based on individual prognostic factors. Combining chemotherapy, immunotherapy, and targeted therapies (e.g., ibrutinib for MYD88-positive cases) is often required for high-risk patients.

Quick Tip

Treatment response and outcomes in WM are significantly influenced by genetic markers such as MYD88 and CXCR4. A tailored, risk-adapted treatment approach improves patient outcomes.

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2. a) Describe the different imaging modalities used in multiple myeloma patients.

Solution:

Step 1: Overview of Imaging Modalities.
In multiple myeloma (MM) patients, various imaging modalities are used to assess bone involvement, disease progression, and response to treatment. The most commonly used imaging techniques include: 1. **X-ray (Radiography):** X-rays are the traditional method for detecting bone lesions in MM, particularly lytic bone lesions. However, they are less sensitive compared to modern techniques.
2. **Magnetic Resonance Imaging (MRI):** MRI is used to detect both bone marrow involvement and soft tissue lesions. It is more sensitive than X-rays for identifying early bone marrow changes and extramedullary disease.
3. **Positron Emission Tomography (PET)/CT:** PET/CT combines the functional imaging of PET with the anatomic detail of CT. It is particularly useful for detecting extramedullary disease and assessing the metabolic activity of lesions. PET/CT is commonly used to monitor response to treatment.
4. **Computed Tomography (CT):** CT scans provide detailed images of bones and are used for detecting bone destruction and extramedullary disease. They are more sensitive than X-rays but have higher radiation exposure.

Quick Tip

MRI and PET/CT are superior to X-rays for detecting early bone marrow involvement and extramedullary disease in multiple myeloma.

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2. b) Discuss the sensitivity and specificity of these imaging modalities.

Solution:

Step 1: Sensitivity and Specificity Overview.
Sensitivity refers to the ability of a test to correctly identify those with the disease (true positives), while specificity refers to the ability of the test to correctly identify those without the disease (true negatives). The sensitivity and specificity of imaging modalities in MM vary: 1. **X-ray (Radiography):** X-rays have a relatively low sensitivity (about 50-70%) for detecting early bone lesions, meaning they may miss small or early-stage lesions. Their specificity is higher, meaning they are good at confirming large lesions, but they are not as useful for detecting minimal or early disease.
2. **MRI:** MRI is highly sensitive (approximately 80-90%) for detecting bone marrow involvement, making it an excellent tool for early diagnosis. However, its specificity can be lower, as it may pick up non-specific changes that are not related to myeloma.

3. **PET/CT:** PET/CT has high sensitivity for detecting metabolic activity in lesions, including extramedullary disease. Its specificity is also high, as it can differentiate between active disease and benign processes. PET/CT is especially valuable in detecting relapse or residual disease.
4. **CT:** CT scans are highly sensitive for detecting structural bone lesions and are useful for identifying areas of cortical bone destruction. Their specificity is also good, but CT is not as sensitive for detecting soft tissue lesions compared to MRI.

> Quick Tip
>
> MRI and PET/CT have high sensitivity for detecting early and active disease, making them valuable in assessing multiple myeloma, especially for soft tissue and extramedullary involvement.

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2. c) How are they optimally used in different scenarios in multiple myeloma?

Solution:

Step 1: Optimal Use of Imaging Modalities.
Each imaging modality has its strengths and is optimally used in specific clinical scenarios in multiple myeloma: 1. **X-ray:** X-rays are typically used in the initial assessment of bone involvement in MM and for detecting lytic bone lesions. However, due to their low sensitivity for early disease, they are used less frequently for staging or monitoring treatment response.
2. **MRI:** MRI is the modality of choice for assessing bone marrow involvement, especially in patients with suspected early disease or unexplained anemia. It is also used for detecting spinal cord compression, which is a potential complication of MM. MRI is valuable for evaluating treatment response in the bone marrow.
3. **PET/CT:** PET/CT is particularly useful for staging MM, detecting extramedullary disease, and monitoring disease activity. It is also beneficial for assessing response to therapy and identifying relapses, making it a critical tool for evaluating treatment efficacy in both newly diagnosed and relapsed patients.
4. **CT:** CT scans are useful for evaluating complex bone lesions, such as those in the spine or pelvis, and are helpful for detecting extramedullary disease. They are often used when more detailed anatomic information is required, such as in the evaluation of fractures or complications.

Step 2: Scenario-Based Use.
- For newly diagnosed patients, MRI and PET/CT are essential for staging and assessing bone marrow involvement and extramedullary disease.
- For monitoring treatment, PET/CT is preferred due to its ability to evaluate metabolic activity and assess for residual disease.
- For symptomatic patients with bone pain or suspected fractures, CT scans can provide de-

tailed anatomic information to guide management.

> **Quick Tip**
>
> In clinical practice, MRI and PET/CT are preferred for staging and monitoring treatment response, while CT is more useful for detailed anatomic assessment and complication management.

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3. a) Discuss the approach to diagnosis in a patient suspected of having Factor XIII deficiency?

Solution:

Step 1: Understanding Factor XIII Deficiency.
Factor XIII (FXIII) deficiency is a rare bleeding disorder that results in defective fibrin clot stabilization, leading to prolonged bleeding after trauma or surgery. Diagnosis is often challenging, as patients may not exhibit symptoms until later in life. The clinical presentation may include spontaneous or prolonged bleeding episodes, including umbilical bleeding in neonates, easy bruising, and menorrhagia in females.

Step 2: Diagnostic Approach.
The diagnostic workup for Factor XIII deficiency involves: 1. **Clinical history:** Detailed bleeding history, including any spontaneous bleeding, easy bruising, or abnormal bleeding after surgical procedures.
2. **Screening tests:** Standard coagulation tests such as PT, aPTT, and platelet count are usually normal in Factor XIII deficiency. These tests are often used to rule out other bleeding disorders.
3. **Factor XIII activity assay:** The definitive diagnostic test is the measurement of Factor XIII activity. A clot solubility test (e.g., urea clot test) can confirm the diagnosis. Reduced FXIII levels confirm the deficiency.

> **Quick Tip**
>
> Factor XIII deficiency is diagnosed through specific assays measuring FXIII activity, as standard coagulation tests like PT and aPTT are typically normal.

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3. b) What are the therapy options in this patient?

Solution:

Step 1: Therapy for Factor XIII Deficiency.
Management of Factor XIII deficiency aims to prevent bleeding episodes and manage active bleeding. Therapy options include: 1. **Factor XIII concentrate:** The primary treatment for FXIII deficiency is the intravenous administration of Factor XIII concentrate. This helps to replace the deficient factor and stabilize the fibrin clot.
2. **Fresh frozen plasma (FFP):** In emergencies, FFP can be used as a temporary measure to provide FXIII, though it is not as effective as the concentrate.
3. **Supportive care:** Patients with mild deficiency may require treatment only during periods of increased bleeding risk, such as surgery or trauma. Routine monitoring of FXIII levels is essential to guide therapy.

> Quick Tip
>
> The treatment of choice for Factor XIII deficiency is FXIII concentrate, which provides a more reliable and targeted therapy than FFP.

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3. c) How will you care for a woman with Factor XIII deficiency who is planning for pregnancy?

Solution:

Step 1: Preconception Care.
Women with Factor XIII deficiency planning pregnancy should receive preconception counseling to ensure optimal management of their condition. Factors to consider include: 1. **Factor XIII activity testing:** Preconception testing should confirm FXIII levels and adjust treatment accordingly. If levels are low, Factor XIII concentrate should be administered to ensure adequate clot stabilization during pregnancy and childbirth.
2. **Genetic counseling:** If there is a family history of FXIII deficiency, genetic counseling may be recommended to assess the risk of transmitting the disorder to offspring.

Step 2: Pregnancy Management.
During pregnancy, regular monitoring of FXIII levels is essential, as they may fluctuate during this time. The use of Factor XIII concentrate may need to be adjusted based on these levels. The delivery plan should include preparations for possible bleeding complications, especially during labor, as bleeding risks are higher in FXIII-deficient patients.

Step 3: Postpartum Care.
After delivery, careful monitoring for bleeding and prompt administration of Factor XIII concentrate if necessary is crucial. Postpartum hemorrhage (PPH) risk should be assessed, and appropriate precautions should be taken, including the use of FXIII concentrate during delivery

if levels are low.

> **Quick Tip**
>
> Women with Factor XIII deficiency planning pregnancy should ensure optimal management with Factor XIII concentrate, regular monitoring, and careful delivery planning to reduce bleeding risks.

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4. a) Discuss management approach to an elderly, transplant ineligible multiple myeloma patient.

Solution:

Step 1: Understanding the Condition.
Multiple myeloma (MM) in elderly patients presents unique challenges due to comorbidities, frailty, and reduced tolerance to aggressive treatments. Transplant ineligibility is often due to factors such as advanced age, poor performance status, and other health conditions that preclude intensive chemotherapy or autologous stem cell transplantation. The management of these patients requires a more tailored approach, focusing on improving quality of life and controlling disease progression.

Step 2: First-Line Treatment Options.
For elderly, transplant-ineligible patients, treatment options often include: 1. **Melphalan-based chemotherapy:** Melphalan combined with prednisone is a common treatment regimen. This combination is effective in controlling disease while minimizing toxicity in frail patients.
2. **Immunomodulatory drugs (IMiDs) and Proteasome inhibitors:** Lenalidomide and bortezomib are frequently used in combination regimens. These drugs are well-tolerated and effective in inducing remission in elderly patients.
3. **Monoclonal Antibodies:** Daratumumab, a monoclonal antibody targeting CD38, is used in combination with other therapies for improved outcomes in elderly patients.

Step 3: Supportive Care.
Supportive care is a key component of management. This includes managing pain, preventing infections, maintaining bone health, and addressing anemia. Blood transfusions and bisphosphonates can help manage complications of MM such as anemia and bone disease.

> **Quick Tip**
>
> The treatment for elderly, transplant-ineligible MM patients focuses on minimizing toxicity and improving quality of life. Immunomodulatory drugs and proteasome inhibitors are preferred options.

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4. b) How do you decide treatment at first relapse in this patient?

Solution:

Step 1: Identifying Relapse.
Relapse in multiple myeloma is defined by the reappearance of disease activity after an initial period of remission. Clinical signs of relapse may include worsening of symptoms such as bone pain, anemia, or new organ involvement. Laboratory evidence, such as rising monoclonal protein levels, is used to confirm relapse.

Step 2: Treatment Decision Criteria.
When deciding treatment at first relapse in transplant-ineligible elderly patients, factors to consider include: 1. **Previous treatments:** If the patient has already received drugs like lenalidomide and bortezomib, switching to other agents or combinations may be necessary.
2. **Performance status and comorbidities:** Treatment must be chosen based on the patient's ability to tolerate chemotherapy. For frail patients, lower-intensity regimens may be preferred.
3. **Available therapies:** Options include second-line therapies such as carfilzomib (proteasome inhibitor) or pomalidomide (IMiD), or monoclonal antibodies like daratumumab in combination with other agents.

Step 3: Tailored Treatment Approach.
The goal is to reintroduce a regimen that the patient has not been exposed to previously while minimizing side effects. For example, if the patient has received lenalidomide and bortezomib in the first line, alternatives like pomalidomide or daratumumab may be considered for second-line treatment.

> **Quick Tip**
>
> At first relapse, it is important to assess previous therapies, performance status, and available treatment options. Monoclonal antibodies and second-line therapies are often used in relapsed patients.

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4. c) Discuss treatment options for Lenalidomide-refractory or Bortezomib-refractory multiple myeloma patients.

Solution:

Step 1: Understanding Refractoriness.
Lenalidomide-refractory and bortezomib-refractory multiple myeloma refer to cases where the

disease has not responded to or has relapsed after treatment with these agents. Such patients typically have a poor prognosis and require more intensive or novel therapies.

Step 2: Treatment Options.
1. **Pomalidomide:** Pomalidomide, an IMiD, is an effective option for patients who are refractory to lenalidomide. It has shown efficacy in combination with other agents like low-dose dexamethasone.
2. **Carfilzomib:** Carfilzomib is a second-generation proteasome inhibitor with efficacy in patients who are refractory to bortezomib. It can be used in combination with lenalidomide or dexamethasone.
3. **Daratumumab:** Daratumumab is a monoclonal antibody that targets CD38 and is highly effective in relapsed or refractory MM. It can be used alone or in combination with other agents such as pomalidomide or carfilzomib.
4. **Ixazomib:** Ixazomib, an oral proteasome inhibitor, can be used for patients who have become refractory to bortezomib and other proteasome inhibitors. It is typically combined with lenalidomide and dexamethasone.

Step 3: Considerations for Treatment.
Treatment selection should be based on the patient's previous therapies, side effect profile, and comorbidities. For frail or elderly patients, lower-intensity regimens with good efficacy, like pomalidomide or daratumumab-based therapies, should be considered.

> **Quick Tip**
>
> For lenalidomide-refractory or bortezomib-refractory patients, pomalidomide, carfilzomib, and daratumumab are effective options, often used in combination with other agents.

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5. a) A boy with hemophilia A with inhibitors comes to your center after a road traffic accident and requires urgent surgery. How will you manage surgery in this patient?

Solution:

Step 1: Preoperative Management.
In a patient with hemophilia A and inhibitors, managing surgery requires careful planning due to the risk of bleeding. The presence of inhibitors makes it more challenging to control bleeding, as factor VIII therapy may not be effective. The following steps are essential: 1. **Activated recombinant factor VII (rFVIIa):** The primary treatment for bleeding episodes in patients with inhibitors is activated recombinant factor VII (rFVIIa). This can be used to control bleeding during surgery.
2. **Bypassing agents:** Another option is to use bypassing agents like activated prothrombin complex concentrate (aPCC), which can help reduce bleeding by bypassing the blocked factor

VIII activity.
3. **Desmopressin (DDAVP):** If the patient has a mild form of hemophilia A, desmopressin (DDAVP) may be considered to stimulate the release of endogenous factor VIII, though this is less effective in patients with inhibitors.

Step 2: Intraoperative Monitoring.
During surgery, close monitoring of the patient's coagulation status is essential. This may include regular measurements of activated partial thromboplastin time (aPTT), and Factor VII levels to assess hemostasis. The goal is to maintain adequate clotting while avoiding overcorrection that could lead to thrombosis.

> **Quick Tip**
>
> Activated recombinant factor VII (rFVIIa) and bypassing agents are critical in managing surgery for patients with hemophilia A and inhibitors. Careful monitoring is required to prevent both bleeding and thrombosis.

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5. b) How will you manage and monitor the post-operative care in this patient?

Solution:

Step 1: Postoperative Bleeding Risk.
In hemophilia A patients with inhibitors, the risk of bleeding remains elevated postoperatively. Therefore, the management involves preventing and controlling bleeding, while also avoiding complications from treatment.

Step 2: Treatment Options for Postoperative Care.
1. **Bypassing agents:** Continue administering rFVIIa or aPCC in the immediate postoperative period to maintain hemostasis. The dosage and frequency of administration should be adjusted based on the bleeding risk and clinical condition.
2. **Monitoring coagulation parameters:** Monitor the patient closely for any signs of bleeding, including bleeding from surgical sites, internal bleeding, or excessive bruising. Regular laboratory tests, including aPTT and fibrinogen levels, should be used to guide treatment.
3. **Close monitoring in a controlled environment:** Postoperative care should be provided in a setting that allows for continuous monitoring and prompt management of any bleeding or clotting complications.

> **Quick Tip**
>
> After surgery, continue with bypassing agents and closely monitor coagulation parameters. Adjust the treatment based on the patient's clinical status.

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5. c) What long term options are available for prophylaxis in this patient?

Solution:

Step 1: Prophylaxis Strategy in Hemophilia A with Inhibitors.
Long-term prophylaxis in patients with hemophilia A and inhibitors aims to prevent bleeding episodes and improve quality of life. The options for prophylaxis are more limited than in patients without inhibitors.

Step 2: Prophylaxis Options.
1. **Bypassing agents:** For long-term prophylaxis, patients may require regular administration of bypassing agents, such as rFVIIa or aPCC, to prevent bleeding episodes. These treatments help manage bleeding episodes by bypassing the deficiency in factor VIII.
2. **Immune tolerance induction (ITI):** Immune tolerance induction involves the use of high-dose factor VIII concentrates or other therapies to try to reduce or eliminate the inhibitors. However, ITI is not always successful and requires careful monitoring.
3. **Emicizumab:** Emicizumab is a monoclonal antibody that mimics the function of factor VIII. It is a promising treatment for patients with hemophilia A and inhibitors, as it reduces the frequency of bleeding episodes. It can be used for prophylaxis, and is administered subcutaneously.

Step 3: Individualized Approach.
The choice of prophylaxis depends on the individual patient's response to treatment, the severity of the hemophilia, and the presence of inhibitors. Careful follow-up and monitoring are essential to assess treatment efficacy and adjust dosing.

> **Quick Tip**
>
> Long-term prophylaxis for hemophilia A with inhibitors may include bypassing agents, emicizumab, or immune tolerance induction. Careful follow-up is essential to assess the effectiveness of the chosen therapy.

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6. a) Describe the risk stratification of polycythemia vera (PV) patients.

Solution:

Step 1: Overview of Polycythemia Vera (PV).
Polycythemia vera (PV) is a type of myeloproliferative neoplasm characterized by an overproduction of red blood cells, leading to increased blood viscosity and a higher risk of thrombotic events. PV is associated with a mutation in the JAK2 gene (JAK2 V617F). Stratifying risk in

PV patients is crucial for determining appropriate treatment and managing potential complications.

Step 2: Risk Stratification in PV.
The two main factors used for risk stratification in PV are age and the presence of cardiovascular risk factors or thrombosis: 1. **Low Risk:** - Age less than 60 years - No history of thrombosis or cardiovascular events - The patient is generally at a low risk for thrombotic complications. 2. **High Risk:** - Age greater than 60 years - History of previous thrombosis (arterial or venous) - Presence of additional risk factors like hypertension, diabetes, or smoking. These patients are more likely to develop thrombotic complications, including stroke, myocardial infarction, or deep vein thrombosis.

Step 3: Treatment Implications.
The risk stratification helps guide therapy decisions, such as the use of phlebotomy, aspirin, and cytoreductive therapy. High-risk patients are often treated more aggressively with cytoreductive agents like hydroxyurea.

> **Quick Tip**
>
> Risk stratification in PV is based on age, history of thrombosis, and cardiovascular risk factors. High-risk patients require more aggressive management to prevent thrombotic events.

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6. b) Discuss the options for PV therapy in an elderly patient ¿60 years of age.

Solution:

Step 1: Considerations in Elderly PV Patients.
Elderly patients with PV (¿60 years) are at higher risk of complications such as thrombotic events, bleeding, and treatment-related side effects. Treatment must be individualized, balancing efficacy and safety.

Step 2: First-Line Therapy for Elderly PV Patients.
1. **Phlebotomy:** Phlebotomy is the cornerstone of initial treatment for PV, aimed at reducing hematocrit levels and improving blood viscosity. It is well tolerated by elderly patients and should be performed regularly to maintain hematocrit levels below 452. **Aspirin:** Low-dose aspirin is used to reduce thrombotic risk, particularly in those with a history of thrombosis or cardiovascular risk factors.

Step 3: Cytoreductive Therapy.
For elderly patients with high-risk features (e.g., previous thrombosis), cytoreductive therapy may be needed: 1. **Hydroxyurea:** Hydroxyurea is the most commonly used cytoreductive

agent. It reduces hematopoiesis and is generally safe in elderly patients. It is effective in preventing thrombosis but requires monitoring for potential myelosuppression.
2. **Interferon-alpha:** In younger patients, interferon-alpha is preferred for its non-mutagenic properties, but in elderly patients, hydroxyurea remains the preferred option due to better tolerance.

> **Quick Tip**
>
> Elderly PV patients are best managed with phlebotomy and low-dose aspirin. Hydroxyurea is commonly used for high-risk cases, but treatment must be tailored to minimize complications.

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6. c) What are the evidence-based second-line therapies for PV patients?

Solution:

Step 1: Second-Line Therapies in PV.
Second-line therapies for polycythemia vera (PV) are considered when patients are refractory to first-line treatments or cannot tolerate them. These therapies are often used for patients with high-risk features or inadequate response to standard treatments.

Step 2: Available Second-Line Therapies.
1. **Ruxolitinib:** Ruxolitinib is a JAK1/2 inhibitor that has shown efficacy in reducing symptoms, spleen size, and improving hematocrit control in patients with PV, especially those with resistance or intolerance to hydroxyurea. It is now considered an important option for PV patients with resistant or refractory disease.
2. **Busulfan:** Busulfan is an alkylating agent used in patients who cannot tolerate hydroxyurea or ruxolitinib. It can be effective in controlling PV but carries a risk of myelosuppression and long-term complications such as secondary malignancies.
3. **Pomalidomide:** Pomalidomide, an IMiD, is another treatment option for patients with relapsed or refractory PV. It is used in selected cases, particularly when other therapies are ineffective.

Step 3: Considerations for Treatment Choice.
The choice of second-line therapy depends on patient factors, such as age, comorbidities, and previous treatment history. Ruxolitinib is often preferred for patients with splenomegaly and those who have failed other therapies.

Quick Tip

Ruxolitinib is a first-line second-line therapy for PV patients who are resistant to or intolerant of hydroxyurea. Busulfan and pomalidomide are also options for refractory disease.

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7. a) Discuss the role of Azacytidine + Venetoclax (Aza+Ven) regimen in an elderly, frail patient with acute myeloid leukemia.

Solution:

Step 1: Overview of Acute Myeloid Leukemia (AML).
Acute myeloid leukemia (AML) is a hematologic malignancy characterized by the uncontrolled proliferation of myeloblasts in the bone marrow. In elderly, frail patients, the treatment of AML presents challenges due to age-related factors, comorbidities, and poor performance status. Chemotherapy-based regimens may be too toxic, which makes the use of targeted therapies like Azacytidine + Venetoclax (Aza+Ven) an important treatment option.

Step 2: Role of Azacytidine and Venetoclax.
1. **Azacytidine (Aza):** Azacytidine is a hypomethylating agent that works by inhibiting DNA methyltransferase, leading to the reactivation of tumor suppressor genes and a reduction in leukemic cell proliferation. It has shown efficacy in elderly patients with AML, particularly in those who are not candidates for intensive chemotherapy.
2. **Venetoclax (Ven):** Venetoclax is a BCL-2 inhibitor that promotes apoptosis in cancer cells by blocking the anti-apoptotic protein BCL-2, which is often overexpressed in AML. When used in combination with azacytidine, venetoclax has demonstrated improved response rates and survival outcomes in AML patients.
Together, Aza+Ven targets two key pathways in AML: epigenetic modification and apoptosis resistance, making it a promising option for elderly, frail patients.

Step 3: Treatment Benefits.
The Aza+Ven regimen has been shown to improve overall survival and response rates in elderly AML patients, particularly those with adverse cytogenetics or poor prognostic features. It is well-tolerated compared to traditional chemotherapy regimens, offering a less toxic alternative for patients who cannot tolerate intensive therapy.

Quick Tip

The Aza+Ven regimen combines the effects of hypomethylation and apoptosis induction, making it an effective and less toxic treatment option for elderly, frail AML patients.

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7. b) How will you decide treatment after first cycle of Aza+Ven therapy?

Solution:

Step 1: Assessing Response to First Cycle.
After the first cycle of Aza+Ven therapy, the patient's response must be carefully evaluated. Key factors to consider include: 1. **Bone Marrow Response:** The first step is to assess the degree of remission or cytogenetic response using bone marrow biopsy. Complete remission (CR) or partial remission (PR) is considered a positive response. If no response is seen, alternative therapies should be considered.
2. **Peripheral Blood Counts:** A reduction in blast percentage in the peripheral blood indicates a good response. If counts remain high, further adjustments may be required.
3. **Side Effects and Tolerability:** The patient's tolerance to treatment is crucial. Monitoring for adverse effects such as neutropenia, thrombocytopenia, or infections is necessary to determine whether therapy needs to be adjusted.

Step 2: Further Treatment Decisions.
1. **Continued Aza+Ven:** If the patient achieves CR or PR with manageable side effects, continuation of the Aza+Ven regimen for further cycles is recommended.
2. **Alternative Therapy:** If there is no significant response or if the patient experiences intolerable side effects, alternative therapies, such as intensive chemotherapy or other targeted therapies, may need to be considered.

Quick Tip

The decision to continue Aza+Ven therapy after the first cycle depends on the patient's response (CR/PR) and the tolerability of the regimen.

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7. c) What are the options for this elderly patient if he relapses after 2 years while on Aza+Ven treatment?

Solution:

Step 1: Assessing Relapse in AML.
Relapse in AML after initial remission can be challenging, especially in elderly patients. A relapse after 2 years on Aza+Ven treatment requires a careful assessment of the disease burden, genetic mutations, and the patient's overall health.

Step 2: Treatment Options for Relapsed AML.
1. **Reinduction Therapy:** The first option for relapsed AML is reinduction therapy, often using higher doses of chemotherapy, such as a combination of cytarabine and anthracyclines, although this may be less well tolerated in elderly patients.

2. **Ruxolitinib:** For patients with specific mutations (e.g., JAK2), ruxolitinib, a JAK1/2 inhibitor, may be considered, particularly if there is an associated myeloproliferative disorder.
3. **Allogeneic Stem Cell Transplantation:** If the patient is eligible and has a suitable donor, an allogeneic stem cell transplant may be an option, especially for those with high-risk disease or multiple relapses.
4. **Second-Line Targeted Therapy:** If the patient has a specific mutation (e.g., FLT3-ITD), targeted therapy such as midostaurin or gilteritinib could be considered.

Step 3: Palliative Care.
If the patient is not a candidate for reinduction or transplant, palliative care may be appropriate, focusing on symptom management and quality of life.

> Quick Tip
>
> For relapsed AML, options include reinduction chemotherapy, stem cell transplant, or second-line targeted therapies based on the relapse characteristics. Palliative care is an option for non-eligible patients.

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8. a) In Philadelphia positive acute lymphoblastic leukemia (ALL), how is the choice of tyrosine kinase inhibitor (TKI) made?

Solution:

Step 1: Understanding Philadelphia Positive ALL.
Philadelphia chromosome-positive (Ph+ ALL) is a subtype of acute lymphoblastic leukemia (ALL) characterized by the presence of the Philadelphia chromosome, a result of the translocation between chromosomes 9 and 22, leading to the formation of the BCR-ABL fusion gene. This gene encodes for an abnormal tyrosine kinase (BCR-ABL), which plays a key role in leukemogenesis. Tyrosine kinase inhibitors (TKIs) target this abnormal kinase activity, making them a cornerstone of therapy in Ph+ ALL.

Step 2: Choice of Tyrosine Kinase Inhibitor (TKI).
The choice of TKI is made based on the patient's clinical characteristics, prior treatment history, and the presence of mutations within the BCR-ABL kinase domain: 1. **Imatinib:** Imatinib is the first-generation TKI and has been a standard treatment for Ph+ ALL. It is typically used as a frontline therapy and is effective in most patients.
2. **Second-generation TKIs:** For patients who have resistance to imatinib or relapse, second-generation TKIs such as dasatinib and nilotinib are preferred. These drugs have a broader spectrum of action and are more effective against certain mutations in the BCR-ABL gene.
3. **Third-generation TKIs:** In cases of further resistance or mutations such as the T315I mutation, third-generation TKIs like ponatinib are used. Ponatinib is highly effective against resistant mutations but comes with a higher risk of side effects.

Step 3: Resistance and Mutations.
The selection of TKI should be guided by the presence of specific mutations in the BCR-ABL kinase domain. Mutations such as T315I are known to cause resistance to imatinib and second-generation TKIs, necessitating the use of ponatinib. Regular mutation testing and monitoring for resistance are essential for optimizing therapy.

> **Quick Tip**
>
> The choice of TKI in Ph+ ALL depends on mutation testing and prior therapy. Imatinib is first-line, while dasatinib, nilotinib, and ponatinib are used based on resistance or mutation status.

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8. b) Discuss the role of baseline tyrosine kinase domain mutation study in this scenario.

Solution:

Step 1: Importance of Mutation Study.
Baseline tyrosine kinase domain mutation study is crucial for identifying resistance mutations to first-line TKIs such as imatinib. Mutations in the BCR-ABL kinase domain can significantly impact treatment efficacy and guide the choice of second or third-generation TKIs.

Step 2: Key Mutations.
1. **T315I mutation:** This mutation is associated with resistance to imatinib and second-generation TKIs. It is one of the most important mutations to detect as it requires treatment with third-generation TKIs like ponatinib.
2. **F317L, V299L, and M351T mutations:** These mutations can lead to resistance to second-generation TKIs like dasatinib and nilotinib. Detection of these mutations can help in choosing the most effective therapy.
3. **E255K and Y253H mutations:** These mutations are associated with resistance to imatinib but can be sensitive to dasatinib and nilotinib. Mutation testing helps in identifying the right treatment options for these cases.

Step 3: Implications for Treatment.
Mutation studies enable personalized treatment approaches. In patients without resistance mutations, first-line therapy with imatinib is appropriate. However, for patients with resistance mutations, second or third-generation TKIs can be selected based on the specific mutation profile. Regular monitoring for emerging mutations during treatment is also recommended.

Quick Tip

Mutation testing is essential for guiding TKI therapy in Ph+ ALL. Identifying mutations like T315I allows for the use of appropriate second or third-generation TKIs.

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8. c) In an elderly patient with Philadelphia positive ALL, what are the chemotherapy-free treatment options?

Solution:

Step 1: Challenges in Elderly Patients.
Elderly patients with Philadelphia-positive ALL (Ph+ ALL) often have comorbidities, frailty, and reduced tolerance to intensive chemotherapy. Therefore, chemotherapy-free treatment options are preferred to minimize toxicity while effectively managing the disease.

Step 2: Chemotherapy-Free Treatment Options.
1. **Tyrosine Kinase Inhibitors (TKIs):** TKIs such as imatinib, dasatinib, nilotinib, and ponatinib are the mainstay of therapy in Ph+ ALL, and they are used without chemotherapy. These agents target the BCR-ABL fusion protein and block the proliferative signals in leukemic cells. The choice of TKI depends on the presence of mutations and the patient's overall health.
2. **Immunotherapy:** Monoclonal antibodies such as blinatumomab (a bispecific T-cell engager) or inotuzumab ozogamicin (an anti-CD22 antibody-drug conjugate) are increasingly being used in elderly patients with ALL, including Ph+ ALL, to avoid chemotherapy. These agents are effective in reducing the leukemic burden and are well-tolerated in frail patients.
3. **Combination Therapy without Chemotherapy:** In some cases, combining TKIs with immunotherapies (e.g., TKI + blinatumomab) provides effective disease control while minimizing chemotherapy-related toxicity.

Step 3: Considerations for Treatment.
Treatment decisions should be guided by the patient's age, comorbidities, and ability to tolerate systemic chemotherapy. TKIs and immunotherapy can be used as effective, less toxic alternatives to chemotherapy in elderly patients with Ph+ ALL.

Quick Tip

For elderly Ph+ ALL patients, chemotherapy-free options like TKIs and monoclonal antibodies (blinatumomab) provide effective disease control with reduced toxicity.

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9. a) Discuss the role of complement system in coagulation.

Solution:

Step 1: Overview of the Complement System.
The complement system is a part of the innate immune system that consists of a series of proteins that work together to defend against infections, facilitate inflammation, and clear dead cells. It plays an essential role in the regulation of coagulation and fibrinolysis, influencing the formation and dissolution of blood clots.

Step 2: Complement System and Coagulation.
1. **Activation of Coagulation:** The complement system activates coagulation by promoting the activation of prothrombin to thrombin, which is essential for fibrin clot formation. Complement proteins C3a and C5a, through their effects on platelets, can enhance platelet aggregation and the expression of procoagulant factors.
2. **Linking Inflammation and Coagulation:** Complement activation induces the release of pro-inflammatory cytokines, which can lead to the activation of the clotting cascade. This connection between inflammation and coagulation is particularly important in conditions like sepsis, where the complement system plays a role in disseminated intravascular coagulation (DIC).
3. **Regulation of Coagulation:** Complement proteins like C1 inhibitor help regulate the coagulation cascade by preventing excessive activation, which can lead to thrombotic events. Proper regulation ensures a balanced response to injury without triggering unwanted clotting or bleeding.

> Quick Tip
>
> The complement system regulates both coagulation and fibrinolysis. By activating prothrombin and enhancing platelet aggregation, complement plays a crucial role in clot formation.

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9. b) Mention new complement inhibitors used in treatment of paroxysmal nocturnal hemoglobinuria (PNH).

Solution:

Step 1: Overview of Paroxysmal Nocturnal Hemoglobinuria (PNH).
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematologic disorder characterized by hemolysis, thrombosis, and bone marrow failure. PNH is caused by a mutation in the PIGA gene, which affects the expression of complement-regulatory proteins on the surface of red blood cells, leading to uncontrolled complement activation and hemolysis.

Step 2: Complement Inhibitors in PNH.
1. **Eculizumab:** Eculizumab is a monoclonal antibody that inhibits the complement protein

C5, preventing its cleavage into C5a and C5b, which are involved in the formation of the membrane attack complex (MAC) that damages red blood cells in PNH. It is the standard treatment for PNH and reduces hemolysis and associated complications.
2. **Ravulizumab:** Ravulizumab is a newer, longer-acting complement inhibitor that also targets C5. It is similar to eculizumab but has a prolonged half-life, allowing for less frequent dosing (every 8 weeks). It has been shown to be equally effective as eculizumab in treating PNH, with fewer infusions required.
3. **Coversin:** Coversin is a novel complement inhibitor that targets C5, similar to eculizumab, but it is a smaller peptide and is being studied for its potential in treating PNH and other complement-mediated disorders. It is still under investigation but shows promise in early trials.

Quick Tip

Eculizumab and ravulizumab are the main complement inhibitors used in PNH, with ravulizumab offering a longer duration of action and fewer infusions.

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9. c) Discuss role of vaccination in PNH patients who are to be started on complement inhibitor therapies.

Solution:

Step 1: Risk of Infection in PNH.
PNH patients are at an increased risk of infections, particularly meningococcal infections, due to the inhibition of the complement system. Complement activation is crucial for the immune system's defense against certain pathogens, including Neisseria species, which cause meningococcal infections. Inhibition of C5 with eculizumab or ravulizumab impairs this immune defense, increasing susceptibility to life-threatening infections.

Step 2: Vaccination Recommendations.
1. **Meningococcal Vaccination:** It is essential to vaccinate PNH patients against Neisseria meningitidis before initiating complement inhibitor therapy. Ideally, vaccination should be administered at least 2 weeks before starting eculizumab or ravulizumab to ensure sufficient immune response.
2. **Pneumococcal and Haemophilus influenzae Vaccination:** PNH patients should also receive vaccinations for Streptococcus pneumoniae and Haemophilus influenzae type B, as complement inhibition increases the risk of infections from these bacteria.
3. **Annual Influenza Vaccination:** PNH patients should be vaccinated annually against influenza to reduce the risk of respiratory infections, which could further compromise their health due to complement inhibition.

Step 3: Monitoring Post-Vaccination.
After vaccination, it is important to monitor for adequate immune response, particularly for

meningococcal vaccines. In some cases, additional booster doses may be required.

Quick Tip

PNH patients on complement inhibitors must receive meningococcal, pneumococcal, and influenza vaccinations to reduce the risk of infections. Vaccination should be done before starting complement inhibition therapy.

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10. a) Discuss the diagnosis and prognosis of triple-negative myelofibrosis (TN-MF).

Solution:

Step 1: Diagnosis of Triple-Negative Myelofibrosis (TN-MF).
Triple-negative myelofibrosis (TN-MF) is a subtype of primary myelofibrosis characterized by the absence of mutations in the commonly associated genes (JAK2, CALR, and MPL). This condition is diagnosed based on: 1. **Clinical features:** Symptoms of TN-MF often include fatigue, weight loss, splenomegaly, and systemic inflammatory signs.
2. **Bone marrow biopsy:** A key diagnostic tool, which shows hypercellularity, increased reticulin fibrosis, and dysplastic features in hematopoietic cells. However, the absence of JAK2, CALR, or MPL mutations is crucial for confirming TN-MF.
3. **Cytogenetic and molecular testing:** Although TN-MF lacks these mutations, additional genetic abnormalities may be identified using next-generation sequencing or cytogenetic analysis.

Step 2: Prognosis of TN-MF.
The prognosis of TN-MF is generally poor compared to other subtypes of myelofibrosis. It tends to have a more aggressive course, with higher rates of progression to acute myeloid leukemia (AML) and shorter overall survival. Risk factors that contribute to prognosis include: 1. **Fibrosis stage:** More advanced fibrosis in the bone marrow correlates with a worse prognosis.
2. **Age and comorbidities:** Older age and the presence of comorbidities such as cardiovascular disease worsen prognosis.
3. **Mutational burden:** Though TN-MF lacks the common mutations, other mutations detected in genetic screening, such as ASXL1 or EZH2, can influence prognosis.

Quick Tip

TN-MF is diagnosed by the absence of JAK2, CALR, and MPL mutations, with prognosis being worse due to the aggressive nature of the disease.

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10. b) How does it differ from triple-negative essential thrombocytosis in prognosis?

Solution:

Step 1: Triple-Negative Essential Thrombocytosis (TN-ET).
Triple-negative essential thrombocytosis (TN-ET) is another form of myeloproliferative neoplasm characterized by elevated platelet counts and the absence of JAK2, CALR, or MPL mutations. In contrast to TN-MF, TN-ET has a better prognosis and is typically associated with fewer complications, such as thrombosis and hemorrhage.

Step 2: Prognosis Comparison.
1. **TN-MF Prognosis:** TN-MF is more aggressive and is associated with a higher risk of progression to acute myeloid leukemia (AML) and worse overall survival. The prognosis is typically poor, especially in elderly patients.
2. **TN-ET Prognosis:** TN-ET generally has a better prognosis, with a risk of thrombosis being the most common complication. It has a much lower risk of progression to leukemia or myelofibrosis compared to TN-MF. Treatment primarily focuses on controlling the platelet count to reduce thrombotic risks.

Step 3: Key Differences.
- TN-MF is characterized by bone marrow fibrosis and a poor prognosis, while TN-ET is associated with elevated platelets and a more indolent course. - TN-MF is more likely to transform into AML, while TN-ET rarely progresses to more aggressive forms of leukemia.

> Quick Tip
>
> TN-MF has a worse prognosis than TN-ET due to its aggressive nature, including the risk of progression to AML and overall shorter survival.

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10. c) Briefly discuss the genomic landscape of TN-MF.

Solution:

Step 1: Genomic Features of TN-MF.
Triple-negative myelofibrosis (TN-MF) lacks the common mutations typically seen in myelofibrosis, such as JAK2, CALR, and MPL. However, it does exhibit a range of other genetic abnormalities that contribute to its pathogenesis and prognosis. These include: 1. **ASXL1 mutations:** These mutations are frequently found in TN-MF and are associated with worse prognosis and an increased risk of transformation to acute leukemia.
2. **EZH2 mutations:** Mutations in EZH2, which encodes a methyltransferase, are common in TN-MF and have been associated with a more aggressive disease course.
3. **TET2 mutations:** TET2 mutations are also seen in a subset of TN-MF patients and can

play a role in the dysregulation of hematopoiesis.
4. **IDH1/IDH2 mutations:** Mutations in the isocitrate dehydrogenase genes (IDH1/IDH2) have been identified in TN-MF and may contribute to epigenetic alterations in hematopoietic cells.

Step 2: Implications of Genomic Alterations.
These mutations help identify the molecular mechanisms underlying TN-MF and may influence treatment decisions and prognosis. Targeted therapies aimed at specific mutations (e.g., IDH inhibitors) are currently being explored in clinical trials. However, these therapies are still under investigation and are not yet standard in clinical practice for TN-MF.

Quick Tip

ASXL1, EZH2, and TET2 mutations are common in TN-MF and are associated with poor prognosis. These genetic alterations may guide future therapeutic strategies.
