Ministry of Health of Republic of Belarus

Education institution

«Gomel State Medical University»

Chair of Internal Disease №1 with course of endocrinology

It is discussed at the meeting of chair _____2019

Protocol №

METHODICAL REVIEW

for practical classes of foreign students of the 5th course

Subject:

Polycythemia.

Multiple myeloma.

Time: 5 hours

Head of the department__________________
1. **Motivation for learning the topic.**

Hematopoietic diseases are one of the actual health problems. As you know, nowadays, the incidence rate of diseases such as iron deficiency anemia, hemorrhagic diathesis, leukemia remains quite high. Severe forms of the pathology course, accompanied by the development of complications and deaths, deserve special attention. The study of this topic gives knowledge and skills for examining patients, identifying early symptoms of diseases; forms the skills of making a diagnosis, planning and conducting medical and diagnostic interventions, prescribing treatment taking into account the characteristics of the disease, skills in providing first aid in emergency conditions, organizing patient care and rehabilitation of patients. Hemoblastoses - acute and chronic leukemia, are among the pathologies of a tumor nature. Knowledge of clinical symptoms, diagnostic criteria, differential diagnosis will help to suspect this pathology promptly and correctly and refer the patient to a hematologist to allow targeted treatment of this diseases.

2. **Aim of training:** to teach students to diagnostics and treatment of polycythemia, multiple myeloma.

3. **Tasks of training:** to form students' social, personal and professional competencies to provide in practice knowledge about:

   - patient examination methods in case of polycythemia, multiple myeloma;
   - tactics of establishing a diagnosis and differential diagnosis in polycythemia, multiple myeloma;
   - methodology for preparing a patient examination plan;
   - evaluation of the results of laboratory and instrumental studies in polycythemia, multiple myeloma;
   - methods of treatment patients with polycythemia, multiple myeloma;
   - emergency care for diseases of the hematopoietic system.

4. **During the training the student should**

   **To know:**
risk factors, etiology, pathogenesis, classification, clinical presentation, diagnosis and differential diagnosis, principles of treatment and prevention of paraproteinemic hemoblastoses and polycythemia;
-methods of diagnostic, emergency care and medical tactics in case of critical condition of the patient (due to hemorrhages, anemia, infectious complications, thrombosis and thromboembolism);
-rehabilitation methods and principles of medical and social expertise.

To be able:

-conduct a patient examination and evaluate the detected changes from various organs and systems;
-draw up and justify a survey plan for differential diagnosis in case of pain in the heart, heart murmur, cardiomegaly, disturbance of the heart rhythm and conduction, arterial hypotension and hypertension, myocardial damage, lymphadenopathy and splenomegaly, anemia, hemoblastosis, hemorrhagic syndrome, joint damage, fainting, shock, side effects of drugs;
-determine and prescribe the minimum of laboratory and instrumental tests necessary for the diagnosis;
-evaluate and interpret the results of the survey;
-choose the optimal treatment tactic for a particular patient, prescribe individual drug therapy taking into account the mechanism of action, pharmacokinetics and pharmacodynamics of drugs, prevention of their unwanted side effects, possible interaction with the concomitant use of other drugs;
-recommend non-drug therapy;
-choose a form, dose and route of administration of drugs;
-keep medical records (draw up a medical history: examinations, medical detours, diaries, list of appointments);
-make a doctor's prescription for conventional medicines;
-provide emergency medical care for the most common emergency situations in practice;
-ensure continuity in the provision of examination and treatment on outpatient and inpatient levels;
-draw up a rehabilitation program for the patient, monitor its implementation;
-give the patient recommendations on primary prevention, a healthy lifestyle, taking into account his health status;
- use educational, scientific, normative and reference literature;
- comply with the rules of medical ethics and deontology;

**In relation to the topic of this lesson:**

- purposefully clarify complaints and collect anamnesis;
- conduct a medical examination of the patient, evaluate changes in his condition;
- be able to identify the main symptoms;
- highlight the leading symptoms;
- formulate a preliminary diagnosis;
- make a plan of examination;
- evaluate the obtained data of laboratory and instrumental methods of examination and identify changes that are characteristic of hemoblastoses;
- substantiate the clinical diagnosis, formulate it in accordance with the classification;
- prescribe treatment taking into account the peculiarities of the course of the disease, the presence of complications and concomitant pathology;
- provide emergency medical care in case of critical condition of the patient (associated with severe anemia, bleeding, infectious complications, thrombosis and thromboembolism);
- determine blood type and Rh factor;
- determine the indications for conducting of blood transfusion, carry out this procedure in practice;
- give the patient recommendations for primary and secondary prevention of the disease, a healthy lifestyle;
- write prescriptions for medications necessary for further treatment.

5. **Requirements to initial level of knowledge:**

To fully master the topic, the student must repeat from the following disciplines:
1. From the courses of normal physiology, pathological physiology - the modern scheme of hematopoiesis and the factors that regulate it, normal indicators of peripheral blood and bone marrow (according to the hemogram, myelogram), the pathogenesis of hemoblastoses.

2. From the pathological anatomy course - the pathological anatomy of chronic leukemia, multiple myeloma.

3. From the course of pharmacology - pharmacokinetics and pharmacodynamics of cytostatic agents, steroids, anticoagulants, antiplatelet drugs.

4. From the course of propedeutics of internal diseases - the main symptoms and syndromes, examination methods for blood diseases.

6. **Material equipment:**

1. Test control.

2. Situational tasks on the topic of the lesson.

3. The results of instrumental and laboratory examinations of the patients with this pathology.

4. Thematic tables and schemes (illustrating classifications, clinical manifestations, diagnosis and treatment of thematic diseases). The list of drugs used to treat this pathology.


6. Methodological manuals and recommendations on this topic.

7. **Questions from related subjects:**

1. Describe the normal indicators of peripheral blood and bone marrow (according to hemogram, myelogram).

2. Pathological anatomy of leukemia - changes in internal organs in chronic leukemia, multiple myeloma.

3. What are the main causes of leukocytosis, erythrocytosis.

4. Describe the main clinical manifestations of polycythemia, multiple myeloma.

5. What means plethoric syndrome?

8. **Questions on an occupation subject:**
4. Supervision of patients with polycythemia, multiple myeloma, collection of complaints and anamnesis; objective data; survey plan; interpretation of the results of laboratory and instrumental examination methods; diagnosis; treatment plan.

9. Questions for poll of students:

Questions to control the initial level of knowledge:
2. The stages of polycythemia and the main clinical signs. Outcomes of polycythemia.
3. Diagnosis of polycythemia.
4. Symptomatic erythrocytosis. The main reasons for the development.
5. Multiple myeloma. Pathogenesis. The main clinical manifestations.
6. Diagnosis of multiple myeloma.

Questions for the final control of mastering the topic:
1. Differential diagnosis of polycythemia with symptomatic erythrocytosis.

10. Tasks for self-preparation:
Task No. 1. Being at a bed of the patient: a) to study complaints, the disease anamnesis, the life anamnesis; b) to examine the patient; c) to carry out a palpation of area of heart, a percussion, a heart auscultation; d) to investigate arterial pulse; e) to carry out a percussion and an auscultation of lungs; f) to carry out a percussion and a liver and spleen palpation; g) to make a pre-trial detention about existence at the patient any symptoms of the polycythemia, multiple myeloma.

Task No. 2. To carry out the review of patient's records of the patient with an assessment of methods of inspection and treatment: a) to pay attention to emergence of the first symptoms of a disease, hospitalization terms; b) to estimate, whether in sufficient volume laboratory and tool researches are carried out: c) to define a forecast at the patient for life and work capacity.

Task No. 3.
To study patient's records of the patient with the polycythemia, multiple myeloma a) to analyse compliance of preliminary and clinical diagnoses; b) to define severity of a condition of the patient; c) to analyse data of tool methods of research; d) to offer additional methods of inspection; e) to make the plan of treatment of the patient; f) to define a disease forecast for life and work capacity.

Task No. 4.
To give interpretation of results of tool methods of research available for the patient: a) to study the blood tests; b) to study results of x-ray of bones; c) to study data of ultrasound scan of internal organs; d) to study data of sternal puncture; e) to define indications to chemotherapy.

Task No. 5.
Make an examination plan for a patient with severe proteinuria, accelerated ESR, anemia.
For this:
a) Find out complaints, collect a medical history, conduct a physical examination, assess the patient’s condition.
b) Justify the preliminary diagnosis.
c) Make a plan of laboratory and instrumental examination with its justification

Independent work of the student on occupation includes a survey of the patients, work with literature, methodical development on studied subjects

Answers to the questions

POLYCYTHEMIA VERA (PV) is a chronic myeloproliferative disorder characterized by an increased red blood cell mass (RCM), or erythrocytosis, which leads to hyperviscosity and an increased risk of thrombosis.

Epidemiology of polycythemia vera
The average age of patients diagnosed with PV is 60 years, although it can occur in persons in all age groups. PV occurs with a slight predominance in men. The incidence of PV is 2.3 per 100,000 persons per year. Untreated patients may survive for 6 to 18 months, whereas adequate treatment may extend life expectancy to more than 10 years.

**Clinical features of polycythemia vera**

Patients may present with complaints of pruritus after bathing, burning pains in the distal extremities (erythromelalgia), gastrointestinal disturbances, or nonspecific complaints such as weakness, headaches, or dizziness (Table 1).

**Table 1 – Signs and symptoms of polycythemia vera**

<table>
<thead>
<tr>
<th>More common:</th>
</tr>
</thead>
<tbody>
<tr>
<td>hematocrit level &gt; 52 percent (0.52) in white men, &gt; 47 percent (0.47) in Afro-Americans and women;</td>
</tr>
<tr>
<td>hemoglobin level &gt; 18 g per dL (180 g per L) in white men, &gt; 16 g per dL (160 g per L) in Afro-Americans and women);</td>
</tr>
<tr>
<td>plethora;</td>
</tr>
<tr>
<td>pruritus after bathing;</td>
</tr>
<tr>
<td>splenomegaly;</td>
</tr>
<tr>
<td>weight loss;</td>
</tr>
<tr>
<td>weakness;</td>
</tr>
<tr>
<td>sweating.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less common:</th>
</tr>
</thead>
<tbody>
<tr>
<td>bruising/epistaxis;</td>
</tr>
<tr>
<td>Budd-Chiari syndrome;</td>
</tr>
<tr>
<td>erythromelalgia;</td>
</tr>
<tr>
<td>gout;</td>
</tr>
<tr>
<td>hemorrhagic events;</td>
</tr>
<tr>
<td>hepatomegaly;</td>
</tr>
<tr>
<td>ischemic digits;</td>
</tr>
<tr>
<td>thrombotic events;</td>
</tr>
<tr>
<td>transient neurologic complaints (headache, tinnitus, dizziness, blurred vision, paresthesias);</td>
</tr>
<tr>
<td>atypical chest pain.</td>
</tr>
</tbody>
</table>

Other patients are diagnosed after an incidental finding of an elevated hemoglobin and/or hematocrit level on a complete blood count.

**Diagnosis of polycythemia vera**

PV should be suspected when hemoglobin and/or hematocrit levels are elevated (i.e., hemoglobin level greater than 18 g per dL [180 g per L] in white men and 16 g per
dL [160 g per L] in Afro-Americans and women; hematocrit level greater than 52 percent (0.52) in white men and 47 percent (0.47) in Afro-Americans and women). PV also should be suspected in patients with portal venous thrombosis and splenomegaly with or without thrombocytosis and leukocytosis.

**Criteria for polycythemia vera (PV)**

Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria:

- **major criteria:**
  1. hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume;
  2. presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation;
- **minor criteria:**
  1. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation;
  2. serum erythropoietin level below the reference range for normal;
  3. endogenous erythroid colony formation in vitro.

In making the diagnosis of PV, the physician must first exclude a secondary erythrocytosis. Once a secondary cause is ruled out, the diagnosis of PV is made using a combination of major and minor criteria defined by the Polycythemia Vera Study Group (PVSG).

**Secondary causes of increased red cell mass (erythrocytosis)**

- **Physiologically appropriate:**
  - chronic pulmonary or cardiac disease;
  - decreased 2,3-diphosphoglycerate;
  - high oxygen affinity hemoglobinopathy;
  - increased carboxyhemoglobin (in smokers) and methemoglobin;
  - residence at high altitude.
- **Physiologically inappropriate:**
  - adrenal cortical hypersecretion;
  - hydronephrosis;
  - tumors producing erythropoietin or anabolic steroids.
- **Relative (stress):**
  - disorders associated with decreased plasma volume (e.g., diarrhea, emesis, renal diseases).

**New diagnostic modalities to diagnose polycythemia vera:**

- serum erythropoietin (EPO) levels are low or normal;
• bone marrow histopathology and karyotype;
• presence of endogenous erythroid colonies (EEC).

**Treatment of polycythemia vera**

The major goal of treatment is to prevent thrombotic events. Examples of thrombotic events include arterial and venous thrombosis, cerebrovascular accident, deep venous thrombosis, myocardial infarction, peripheral arterial occlusion, and pulmonary infarct. Of additional importance to the family physician is the symptomatic treatment of the bothersome microvascular sequelae, such as pruritus and distal extremity erythromelalgia.

**Table 2 – Symptomatic treatments in polycythemia vera**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>H₁ and H₂ blocking antihistamines (diphenhydramine, cyproheptadine, hydroxyzine, fexofenadine, terfenadine)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Oatmeal or starch baths (in lukewarm water)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Recombinant interferon alfa-2b</td>
<td>C</td>
</tr>
<tr>
<td>Erythromelalgia</td>
<td>Aspirin, 50 to 100 mg daily</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Myelosuppressive agents</td>
<td>C</td>
</tr>
</tbody>
</table>

PV produces microvascular sequelae, the symptoms of which, while not life threatening, can be bothersome to patients. Pruritus, particularly after bathing (aquagenic pruritus) is a common symptom and various treatment options are available. Symptoms such as transient neurologic disturbances may respond to low-dose aspirin therapy. Erythromelalgia is rare, occurring in approximately 3 percent of patients with PV. Low-dose aspirin typically is used, with myelosuppressive therapy reserved for those patients who do not respond.

**Table 3 – Myelosuppressive agents for the treatment of polycythemia vera**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Common side effects</th>
<th>Uncommon side effects</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>Antimetabolite</td>
<td>Anemia, neutropenia, oral ulcers, skin ulcers, hyperpigmentation, nail changes</td>
<td>Leg ulcers, nausea, diarrhea, fever, elevated liver function test results</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Agent</td>
<td>Class</td>
<td>Common side effects</td>
<td>Uncommon side effects</td>
<td>Precautions</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>----------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Recombinant interferon alfa-2b</td>
<td>Myelosuppressive</td>
<td>Influenza-like symptoms, fatigue, anorexia, weight loss, alopecia, headache, nausea, insomnia, body pain</td>
<td>Confusion, depression, autoimmunity, hyperlipidemia</td>
<td>Psychiatric disease, cardiovascular disease</td>
</tr>
<tr>
<td>Radioactive phosphorus (³²P)</td>
<td>Radiopharmaceutical</td>
<td>Anemia, thrombocytopenia, leukopenia, leukemia may develop after treatment</td>
<td>Diarrhea, fever, nausea, emesis</td>
<td>—</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Alkylating agent</td>
<td>Pancytopenia, hyperpigmentation, ovarian suppression</td>
<td>Pulmonary fibrosis, leukemia, seizure, hepatic veno-occlusion</td>
<td>Seizure disorder</td>
</tr>
</tbody>
</table>

The use of myelosuppressive agents such as radioactive phosphorus (³²P), chlorambucil, busulfan, pipobroman, and hydroxyurea in conjunction with phlebotomy has been studied.

Chlorambucil, busulfan, and pipobroman, all alkylating agents, have fallen out of favor because of concerns about rates of iatrogenic leukemia. The myelosuppressive drugs such as ³²P had an initial advantage over phlebotomy alone regarding thrombosis rates during the first three years of treatment. However, this effect disappeared after three years, and rates of thrombosis thereafter were equivalent.

The nonalkylating myelosuppressive agent hydroxyurea is widely used in the treatment of PV, because it is less leukemogenic. Concern regarding the safety of long-term use of hydroxyurea has been noted.

Recombinant interferon alfa-2b reduces myeloproliferation and splenomegaly, and alleviates the symptom of pruritus.

The mainstay of treatment for PV is phlebotomy, which is aimed at reducing hyperviscosity by decreasing the venous hematocrit level to less than 45 percent (0.45) in white men and 42 percent (0.42) in blacks and women. A recent survey of physicians who were members of the American Society of Hematology showed that 69 percent use phlebotomy as first-line therapy for PV.

A number of new therapeutic agents have been developed. In addition to interferon alfa-2b therapy, agents that target platelet number (e.g., anagrelide), and platelet function (e.g., aspirin) are being investigated as potential therapies.
MULTIPLE MYELOMA (MM) is characterised by uncontrolled proliferation of plasma cells within the marrow (mature antibody producing B cells).

Epidemiology of multiple myeloma

The annual incidence of MM is \( \sim 4 \) per 100 000 inhabitants. It constitutes 1% of malignant diseases and almost 15% of all haematological malignancies. The incidence in blacks is twice that in whites. The peak of higher incidence is between 60 and 70 years of age. Only 15% and 2% of patients are younger than 50 and 40 years, respectively. It is evident that MM is an age-related disease but the ultimate cause is unknown.

It has been recently recognized that virtually all cases of MM are preceded by monoclonal gammopathy of undetermined significance (MGUS) (an asymptomatic condition with an M-protein concentration of \(<3\) g/dl and \(<10\)% bone marrow plasma cells (BMPCs). However, the cause of MGUS, the precise mechanisms that maintain the MGUS state and the mechanisms that trigger progression from MGUS to MM are still unknown.

Diagnosis of multiple myeloma

The features of end-organ damage are defined as follows: hypercalcemia, renal insufficiency, anemia, and/or bone disease manifested by osteolytic lesions or osteoporosis. Osteolytic lesions are most commonly found in the axial skeleton, skull, shoulder girdle, proximal humeri, ribs, and proximal femurs. Additionally, patients may present with multiple extramedullary plasmacytomas at diverse sites, including the nasopharynx, larynx, and upper respiratory tract.

According to current diagnostic criteria, multiple myeloma is diagnosed in the presence of a monoclonal protein detectable in the blood or urine, light chain restricted plasma cells in the bone marrow, and myeloma-related end-organ damage.

**Diagnosis** is based on laboratory and radiographic findings and depends on 3 abnormal results:
- bone marrow containing more than 10% plasma cells (normally no more than 4% of the cells in the bone marrow are plasma cells);
- generalised osteopaenia and/or lytic bone deposits on plain film radiography;
- blood serum and/or urine containing an abnormal protein.

In about 75% of all cases of multiple myeloma the paraprotein present (M protein) will correspond with one type of immunoglobulin. In about 60% of cases an abnormal protein, known as Bence-Jones protein may also be found in the urine. Measuring the amount of paraprotein in the blood or urine is of value in the diagnosis of myeloma and in monitoring the response to treatment. A full list of criteria for diagnosis issued by the International Myeloma Working Group can be found elsewhere.

Staging of multiple myeloma
The clinical staging system devised by Durie and Salmon distinguishes different patient subgroups in terms of tumour mass and disease aggression and still often determines management. Patients with at least 2 lytic foci are classified in advanced disease subgroups and aggressive systemic treatment is usually indicated. Subsequently, the scientific advisers of the International Myeloma Foundation proposed a new staging system called Durie and Salmon PLUS based on the traditional Durie and Salmon system integrated by fluorodeoxyglucose (FDG)-positron emission tomography (PET) or magnetic resonance imaging (MRI) of the spine. This staging system has recently been replaced by the one based entirely on serum β2 microglobulin and serum albumin levels. However, this system cannot be used for therapeutic risk stratification and does not provide a good estimate of tumour burden.

**Table 4 – Durie–Salmon PLUS staging system for symptomatic multiple myeloma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Imaging findings (including MR and FDG PET)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I clinical criteria</td>
<td>&lt;5 focal spine lesions ± mild diffuse spine disease</td>
</tr>
<tr>
<td>Stage II clinical criteria</td>
<td>5-20 focal lesions ± moderate diffuse spine disease</td>
</tr>
<tr>
<td>Stage III clinical criteria</td>
<td>&gt;20 focal lesions ± severe diffuse spine disease</td>
</tr>
</tbody>
</table>

**Table 5 – New international staging system of multiple myeloma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum β2 microglobulin criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Serum β2 microglobulin &lt;3.5 mg/l (average survival 62 months), serum albumin &gt;3.5 g/dl</td>
</tr>
<tr>
<td>Stage II</td>
<td>Not I or III(^a) (average survival 44 months)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Serum β2 microglobulin &gt;5.5 mg/l (average survival 29 months)</td>
</tr>
</tbody>
</table>

\(^a\)There are 2 categories for stage II: serum β2 microglobulin <3.5 mg/l but serum albumin <3.5 g/dl or serum β2 microglobulin 3.5–5.5 mg/l irrespective of the serum albumin level.

**Radiology and cross-sectional imaging**

Radiology plays an important role in staging, monitoring treatment response, detection of relapse and assessing complications.

**Conventional radiography (skeletal survey)**

Almost 80% of patients with multiple myeloma have radiological evidence of skeletal involvement at diagnosis manifest in 4 different appearances: solitary deposit (plasmacytoma), diffuse skeletal involvement (myelomatosis), generalised osteopaenia and sclerosing myeloma. Views acquired should be posterior-anterior chest, anterior-posterior (AP) and lateral views of cervical spine (including an open mouth view), thoracic spine, lumbar spine, humeri and femora, AP and lateral views of skull and AP
view of pelvis. Additional views of any symptomatic area should also be acquired. The most common sites include the vertebrae, ribs, skull and pelvis; involvement of the distal bones is unusual. In early stage disease the role of the plain radiograph is limited with myeloma deposits often not visualised.

Myeloma lesions are sharply defined as small lytic areas (average size 20 mm) of bone destruction with no reactive bone formation. At post mortem these lesions are due to nodular replacement of marrow and bone by plasma cells. Although myeloma arises within the medulla, disease progression may produce infiltration of the cortex, invasion of the periosteum and large extraosseous soft tissue masses. The pattern of destruction may be geographic, moth eaten or permeated. Pathological fractures are common.

Generalised osteopaenia may be the only bone manifestation of myeloma in up to 15% of patients. At post mortem these patients show diffuse replacement of marrow with plasma cells but have less severe bone resorption compared with lytic deposits. Vertebral body collapse is the usual manifestation of this subtype which should not be confused with non-myelomatous osteoporosis that occurs in many older patients.

**Radionuclide imaging**

In multiple myeloma the osteoblastic response to bone destruction is negligible and the bone scan (using technetium-99m labelled diphosphonate) is often therefore normal or may show areas of decreased uptake (photopaenia). As a result its routine use is not recommended. However, skeletal scintigraphy may be helpful in evaluating areas not well visualised on plain film radiographs such as the ribs, sacrum, scapulae and sternum.

PET using the glucose analogue [F]FDG has the functional and morphological capacity to identify the extent and activity of multiple myeloma for staging and monitoring purposes. The ability of PET to perform whole-body examinations is a major advantage over conventional imaging techniques.

**Cross-sectional imaging**

A wide range of findings have been described in CT of myeloma. These include sharp, lytic foci of small and relatively homogeneous size with no sclerotic rim, diffuse faint osteolysis fan angioma-like appearance due to the presence of thickened vertical trabeculae and expansile deposits. CT can accurately depict the extent of associated soft tissue masses and can direct needle biopsy for histological diagnosis. Multidetector CT (MDCT) provides more detailed information on the risk of vertebral fractures compared with conventional radiography and MRI. In patients who are severely disabled or who are unable to undergo MRI examination this is a useful alternative imaging technique.

**Magnetic resonance imaging**

MRI has high sensitivity and its ability to directly visualise bone marrow. The role of MRI (and PET imaging) is acknowledged by their inclusion in the Durie-Salmon PLUS staging system.
The imaging patterns in multiple myeloma can be classified as normal, focal, diffuse and variegated.

**Functional MRI**

Analysis of enhancement patterns following intravenous contrast has enabled a functional component to MRI studies. Changes in microcirculation patterns using MRI circulation parameters (amplitude $A$, exchange rate constant $k_{ep}$) reflecting vascular volume and permeability allow them to be visualised.

Bone marrow angiogenesis is increased in multiple myeloma and has prognostic importance. Patients with newly diagnosed multiple myeloma have higher microvessel density at bone marrow biopsy than do control subjects.

**Uncommon variants of myeloma**

**Extraosseous myeloma**

Clinical manifestations of extraosseous myeloma are rare, occurring in less than 5% of patients with multiple myeloma. Extraosseous myeloma deposits have been reported at multiple sites with the breast, lymph nodes and spleen most frequently involved. It may also occur in the epidural region causing cord compression. Extraosseous myeloma is more aggressive, occurs in a younger age group (average age 50 years) and is associated with worse survival than conventional myeloma.

**Sclerotic myeloma**

Primary sclerotic manifestations are rare and occur only in 3% of patients. It may take the form of diffuse osteosclerosis, patchy sclerotic areas throughout the skeleton or very small numbers of focal sclerotic lesions.

**Therapy of multiple myeloma**

The International Myeloma Foundation and UK Myeloma Forum (with the support of the British Committee for Standards in Haematology) should be regarded as the preferred source of detailed guidance on treatment.

**Treatment strategy is:**
- adequate analgesia;
- rehydration;
- management of hypercalcaemia;
- management of renal impairment;
- treatment of infection.

The response categories (complete, near complete, partial, minimal, stable and progressive) are determined primarily by the level of M protein present. M protein is the level of monoclonal protein measured by protein electrophoresis in serum or 24-h urine.
**Chemotherapy** is indicated for management of symptomatic myeloma. High-dose therapy using melphalan and prednisolone can produce complete remission in up to 75% of patients.

A newer class of drug, bortezomib (a proteasome inhibitor), is effective for treatment of relapsed refractory myeloma and is superior to dexamethasone in progression-free and overall survival. Other new agents entering clinical trials include conventional drugs (doxorubicin), cytokines (bevacizumab), biological agents (β-alanyl cysteamine disulfide) and agents such as arsenic trioxide.

The most serious morbidity in these patients arises from destructive bone deposits which cause severe intractable pain and pathological fractures often resulting in deformity and disability. A recently published retrospective review of outcome data from 67 myeloma patients treated with vertebroplasty showed significant improvement in rest pain, activity pain, narcotic use and mobility. The bisphosphonate group of drugs bind to bone at sites of active bone remodelling and can therefore inhibit myelomatous bone damage arresting the destructive cycle. These agents (used in conjunction with cytotoxic chemotherapy) have been found to be superior to chemotherapy alone in decreasing the incidence of pathological fractures and bone pain and may lead to prolonged survival.

**Autologous transplantation** has an established place in the treatment of myeloma. It is the treatment of choice for patients aged under 65 years and can be considered in older age groups (with good performance status) carrying a procedure-related mortality of less than 5%.

**Radiation therapy** is reserved for patients with spinal cord compression secondary to vertebral body collapse associated with a soft tissue mass or pathological fractures elsewhere associated with a soft tissue mass. It can be very effective but permanently destroys normal bone marrow stem cells in the treatment field.

**New generation of antmyeloma drugs:** IMIDs, pomalidomide, proteasome inhibitors, PR-171, NPI-0052, histone deacetylase inhibitors, SAHA, LBH589, depsipeptide, m-Tor inhibitors, rapamycin, temsirolimus, everolimus, perifosine, monoclonal antibodies, anti-IL-6- CNTO 328, anti-CS1.

Myeloma is generally considered incurable. It is a slowly progressing disease with long periods of relative inactivity. Relapse occurs in virtually all cases. On current treatment regimens patients younger than 70 years can expect a median survival of 5 years (depending on stage). Death results from bacterial infection, renal insufficiency and thromboembolism.

**Supportive therapy of multiple myeloma**

Patients receiving thalidomide or lenalidomide in combination with high-dose glucocorticoids and/or a cytotoxic agent should receive thromboprophylaxis, because of the increased incidence of thromboembolic events.
Peripheral neuropathy is the main adverse effect of regimens containing thalidomide and bortezomib and careful dose reductions and/or drug discontinuation should be considered. In patients receiving bortezomib herpes zoster prophylaxis with aciclovir is mandatory.

An intravenous bisphosphonate (pamidronate or zoledronic acid) can improve or prevent skeletal complications. It is recommended that bisphosphonates be administered for 1 or 2 years after the initiation of primary therapy and during treatment of the active phases of the disease. Their long-term use can result in osteonecrosis of the jaw.

In patients with a serum Hb of <10 g/dl treatment with erythropoietin in order to maintain a serum Hb level of ~12 g/dl should be administered according to the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) recommendations.

**WALDENSTRÖM MACROGLOBULINEMIA**

Waldenström macroglobulinemia (WM) is a B-cell lymphoproliferative disorder characterized by a lymphoplasmacytic infiltration in the bone marrow or lymphatic tissue and a monoclonal immunoglobulin M protein (IgM) in the serum.

**Epidemiology of Waldenström macroglobulinemia**

The overall incidence of Waldenström macroglobulinemia is approximately 5 cases per 1 million persons per year, and this disease accounts for approximately 1% to 2% of hematologic cancers. The incidence of Waldenström macroglobulinemia is highest among white people and is rare in other population groups. The median age at diagnosis varies between 63 and 68 years, and most patients (55%-70%) with a newly diagnosed disease are men.

In the WHO classification, WM is associated with lymphoplasmacytic lymphoma (LPL); it is a clinicopathologic entity characterized by a monoclonal expansion of predominantly small B-lymphocytes with variable plasmacytoid differentiation.

Clinical symptoms WM are hyperviscosity or neuropathy. Hyperviscosity syndrome is usually manifested by bleeding, blurring or loss of vision, dizziness, headache, and neurologic symptoms. Malignant infiltration of the CNS (Bing-Neel syndrome) is uncommon.

**Diagnostic criteria for Waldenström macroglobulinemia**

- IgM monoclonal gammopathy of any concentration;
- bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation;
- intertrabecular pattern of bone marrow infiltration;
- cell surface markers IgM+, CD5+, CD10−, CD19+, CD20+, CD23− in any variations.
**Treatment of Waldenström macroglobulinemia**

The optimal management of patients with newly diagnosed Waldenström macroglobulinemia can be broadly divided into the following components:

1. confirmation of the diagnosis;
2. stratification of risk and determination of the need for treatment;
3. selection of the appropriate initial therapy;
4. choice of additional therapy if initial response is inadequate or the patient’s disease progresses.

Initially, the standard therapy for patients with Waldenström macroglobulinemia was treatment with oral alkylating agents such as chlorambucil, melphalan, or cyclophosphamide.

Combinations of alkylating agents with or without vinca alkaloids or anthracyclines have been used. Alkylating agent–based regimens in combination with rituximab may be preferable as initial therapy for Waldenström macroglobulinemia.

**DRC regimen** consisting of 20 mg of *dexamethasone* administered intravenously followed by *rituximab* intravenously at 375 mg/m² on day 1 and *cyclophosphamide* orally at 100 mg/m² twice daily on days 1 to 5 every 21 days for 6 months in previously untreated patients with symptomatic Waldenström macroglobulinemia.

1. Patients with IgM MGUS or smoldering (asymptomatic) Waldenström macroglobulinemia and preserved hematologic function should be observed without initial therapy.
2. Patients with symptomatic Waldenström macroglobulinemia and modest hematologic compromise, IgM-related neuropathy requiring treatment, or hemolytic anemia unresponsive to corticosteroids should receive standard doses of rituximab alone without maintenance therapy.
3. Patients with Waldenström macroglobulinemia who have severe constitutional symptoms, profound hematologic compromise, bulky disease, or hyperviscosity should be treated with the DRC regimen. Any patient with symptoms of hyperviscosity should first undergo plasmapheresis.

For patients who experience relapse after a response to initial therapy of more than 2 years' duration, the original therapy should be repeated. For patients who had an inadequate response to initial therapy or a response of less than 2 years' duration, an alternative agent or combination should be used. Autologous stem cell transplant should be considered in all eligible patients with relapsed disease.

**REFERENCES**

**Basic**


Additional

7. Scopus [Electronic resource] / Mode of access: https://www.scopus.com