Ministry of Healthcare of Ukraine

Poltava State Medical University

«Approved»
at the meeting of the
Chair of Internal medicine №1
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Methodical instruction for the teachers

Subject	**Internal medicine**
Module №1	**FUNDAMENTALS OF INTERNAL MEDICINE**
Topic	**Lymphomas. Multiple myeloma**
Course	**IV**
Faculty	**Medical**

***The subject of the lesson*: Lymphomas. Multiple myeloma**

Multiple myeloma is a debilitating malignancy that is part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. First described in 1848, multiple myeloma is a disease characterized by a proliferation of malignant plasma cells and a subsequent overabundance of monoclonal paraprotein. An intriguing feature of multiple myeloma is that the antibody-forming cells (ie, plasma cells) are malignant and, therefore, may cause unusual manifestations.

The presentation of multiple myeloma can range from asymptomatic to very symptomatic with complications requiring emergent treatment. Systemic ailments include bleeding, infection and renal failure, and local catastrophes, including pathologic fractures and spinal cord compression. Although patients benefit from treatment (ie, longer life, less pain, fewer complications), currently no cure exists. Recent advances in therapy have helped to lessen the occurrence and severity of adverse effects of multiple myeloma.

The term **lymphoma** describes a heterogenous group of malignancies with different biology and prognosis. In general lymphomas are divided into 2 large groups of neoplasms, namely non-Hodgkin lymphoma (NHL) and Hodgkin disease. About 85% of all malignant lymphomas are NHLs. The median age at diagnosis is the sixth decade of life, with some exceptions. (Burkitt lymphoma and lymphoblastic lymphoma occur in younger patients.) NHL includes many clinicopathologic subtypes, each with distinct epidemiologies; etiologies; morphologic, immunophenotypic, genetic, and clinical features; and responses to therapy.

The aims of the training course:

To know:

- etiology and pathogenesis of multiple myeloma, NHLs.
- classification of multiple myeloma and NHLs
- the basic clinical syndromes multiple myeloma and NHLs
- differential diagnosis multiple myeloma and NHLs
- main principles of treatment multiple myeloma and NHLs

To be able:

- to take anamnesis from patients
- to survey the patient, to reveal and to give the estimation to the changes of the patient’s condition
- to draw up a plan of additional investigations to estimate their results
- to prescribe proper treatment

Contents of the training materialsMultiple Myeloma

Pathophysiology. Multiple myeloma can cause a wide variety of problems. The proliferation of plasma cells may interfere with the normal production of blood cells,

resulting in leukopenia, anemia, and thrombocytopenia. The cells may cause soft-tissue masses (plasmacytomas) or lytic lesions in the skeleton. Feared complications of multiple myeloma are bone pain, hypercalcemia, and spinal cord compression. The aberrant antibodies that are produced lead to impaired humoral immunity, and patients have a high prevalence of infection, especially with encapsulated organisms. The overproduction of these antibodies may lead to hyperviscosity, amyloidosis, and renal failure.

Race. Multiple myeloma accounts for 1.1% of the malignancies in white US residents and 2.1% of the malignancies in black residents.

Sex. The male-to-female ratio of multiple myeloma is 3:2.

Age. The median age of patients with multiple myeloma is 68 years for men and 70 years for women

History. Presenting symptoms of multiple myeloma include bone pain, pathologic fractures, weakness, anemia, infection (often resulting from pneumococcal infection), hypercalcemia, spinal cord compression, or renal failure. Increasingly, physicians are identifying asymptomatic patients through routine blood screening. Typically, a large gap between the total protein and the albumin levels observed on an automated chemistry panel suggests a problem (ie, protein minus albumin equals globulin).

- Bone pain
  - This is the most common presenting symptom in multiple myeloma. Most case series report that 70% of patients have bone pain at presentation.
  - The lumbar vertebrae are one of the most common sites of pain.
- Pathologic fractures and bone lesions
  - Pathologic fractures are very common in multiple myeloma; 93% of patients have more than one site of bony involvement.
  - A common presentation is a severe bony event.
- Spinal cord compression
  - The symptoms that should alert physicians to consider spinal cord compression are back pain, weakness, numbness, or dysesthesias in the extremities. The most common cause of weakness in patients with multiple myeloma is anemia, which may be quite severe.
  - Patients who are ambulatory at the start of therapy have the best likelihood of preserving function and avoiding paralysis.
  - This complication occurs in approximately 10-20% of patients with multiple myeloma at some time during the course of disease.
- Bleeding
  - Occasionally, a patient may come to medical attention for bleeding resulting from thrombocytopenia.
  - In some patients, monoclonal protein may absorb clotting factors and lead to bleeding, but this development is rare.
- Hypercalcemia
  - Patients may have hypercalcemia if they present with confusion, somnolence, bone pain, constipation, nausea, and thirst.
  - This complication may be present in as many as 30% of patients with multiple myeloma at presentation. In most solid malignancies, hypercalcemia

carries an ominous prognosis, but in multiple myeloma, its occurrence does not adversely affect survival.

- Infection
  - Abnormal humoral immunity and leukopenia may lead to infection.
  - Pneumococcal organisms are commonly involved, but shingles (ie, herpes zoster) and *Haemophilus* infections are also more common among patients with multiple myeloma.
- Hyperviscosity
  - Epistaxis may be a presenting symptom of multiple myeloma with a high tumor volume. Occasionally, patients may have such a high volume of monoclonal protein that their blood viscosity increases, resulting in complications such as stroke, myocardial ischemia, or infarction.
  - Patients may report headaches and somnolence, and they may bruise easily and have hazy vision. Patients with multiple myeloma typically experience these symptoms when their serum viscosity is greater than 4 times that of normal serum.
- Neurologic symptoms
  - Carpal tunnel syndrome is a common complication of myeloma.
  - Meningitis (especially that resulting from pneumococcal or meningococcal infection) is more common in patients with multiple myeloma.
  - Some peripheral neuropathies have been attributed to multiple myeloma.

Physical

- Patients with multiple myeloma may have pallor resulting from anemia.
- Patients may have ecchymoses or purpura resulting from thrombocytopenia.
- Bony tenderness is not uncommon in multiple myeloma, resulting from focal lytic destructive bone lesions or pathologic fracture. Pain without tenderness is typical.
- Neurologic findings may include a sensory level change (ie, loss of sensation below a dermatome corresponding to a spinal cord compression), weakness, or carpal tunnel syndrome.
- Extramedullary plasmacytomas, which consist of soft-tissue masses of plasma cells, are not uncommon. Plasmacytomas have been described in almost every site in the body. Although the aerodigestive tract is the most common location, reports also describe orbital, ear canal, cutaneous, gastric, rectal, prostatic, and retroperitoneal lesions.
- Amyloidosis may develop in some patients with multiple myeloma. The characteristic physical examination findings that suggest amyloidosis include the following:

Salmon-Durie staging system for multiple myeloma[8]

- Stage I
  - Hemoglobin level greater than 10 g/dL
  - Calcium level less than 12 mg/dL
  - Radiograph showing normal bones or solitary plasmacytoma
  - Low M protein values (ie, IgG <5 g/dL, IgA <3 g/dL, urine <4 g/24 h)

- Stage II involves criteria that fit neither stage I nor stage III.
- Stage III
  - Hemoglobin level less than 8.5 g/dL
  - Calcium level greater than 12 mg/dL
  - Radiograph showing advanced lytic bone disease
  - High M protein value (ie, IgG >7 g/dL, IgA >5 g/dL, urine >12 g/24 h)
- Subclassification A involves a creatinine level less than 2 g/dL.
- Subclassification B involves a creatinine level greater than 2 g/dL.

International Staging System for multiple myeloma

- Stage I
  - Beta-2 microglobulin less than or equal to 3.5g/dL and albumin >3.5g/dL
- Stage II
  - Beta-2 microglobulin <3.5g/dL and Albumin <3.5 g/dL
  - OR Beta-2 microglobulin level >3.5 to <5.5 g/dL
- Stage III
  - Beta-2 microglobulin >5.5 g/dL

<u>CRAB criteria of ACTIVE/SYMPTOMATIC Multiple Myeloma</u>

C – Calcium – Hypercalcaemia: serum calcium >11.5 mg/dl

R – Renal insufficiency: serum creatinine >1.73 µmol/l (or >2 mg/dl) or estimated creatinine clearance

A – Anaemia: normochromic, normocytic with a haemoglobin value of ≥2 g/dl below the lower limit of normal or a haemoglobin value <10g/dl

B – Bone lesions: lytic lesions, severe osteopenia or pathologic fractures

Active (symptomatic) myeloma treatment

The drugs chosen depend on the patient's health (including their kidney function) and whether a transplant is planned.

Often, a combination containing bortezomib 1.3 mg/m^2 IV or SC on the 1, 4, 8, 11 days, thalidomide 100-200 mg per os every day – 21 days, and dexamethasone 40 mg/day 1, 2, 4, 5, 8, 9, 11, 12 days is used, from 6 to 8 cycles of chemotherapy. Combinations containing bortezomib are especially helpful in patients with kidney problems and those whose myeloma cells contain certain high risk chromosome abnormalities.

Bisphosphonate treatment is often started along with chemo. If the areas of damaged bone continue to cause symptoms, radiation therapy may be used.

A stem cell transplant may be part of treatment.

Some patients are given additional cycles of treatment after transplant. This is called *consolidation treatment* and increases the chance of a complete response.

Some patients (even some who didn't have a stem cell transplant) may be given long-term treatment with thalidomide, lenalidomide, or bortezomib. This is known as *maintenance treatment*, and helps delay the return of the myeloma, but it can cause serious side effects.

Non-Hodgkin Lymphomas (NHLs)

NHLs are a heterogenous group of lymphoproliferative malignancies with varying morphologic features depending on the specific type of this disorder. The abnormal lymphocytes in the lymph node, bone marrow, or extranodal sites can be small cleaved or noncleaved, intermediate, or large cell and can have a follicular or diffuse pattern. In contrast with reactive follicular hyperplasia, lymphomas usually alter the lymph node architecture, and the capsule is usually involved.

NHLs are divided into more than 30 types, classified based on the type of lymphocyte involved: B lymphocytes (B cells) or T lymphocytes (T cells). Further classified by other factors, including whether they are aggressive (fast-growing) or indolent (slow-growing).

Aggressive lymphomas include:

- Diffuse large B-cell lymphoma
- Anaplastic large-cell lymphoma
- Burkitt lymphoma
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Peripheral T-cell lymphoma

Indolent lymphomas include:

- Follicular lymphoma
- Cutaneous T-cell lymphoma
- Lymphoplasmacytic lymphoma
- Marginal zone B-cell lymphoma
- MALT lymphoma
- Small-cell lymphocytic lymphoma

Indolent NHL is a low-grade NHL, meaning the tumour grows very slowly and patients often do not show symptoms until late in the disease. As a result, indolent NHL tends to be widespread at the time of diagnosis. Patients diagnosed with indolent NHL often do not require immediate treatment, and a watchful waiting approach is often employed. Treatment is eventually required and is usually effective at shrinking tumours and giving the patient a disease-free period, called remission. However, indolent NHL may relapse and subsequent rounds of treatment are often required. Sometimes low-grade, indolent NHL will transform into an intermediate or high-grade (aggressive) lymphoma, at which point the patient will require more urgent, intensive treatment. However, patients with indolent NHL often live for a long time and enjoy a good quality of life, and some patients may never even require treatment.

Intermediate and high-grade NHLs generally grow a lot faster than the indolent lymphomas, and for this reason they are referred to as aggressive, or fast-growing lymphomas. Unlike indolent lymphomas, aggressive NHLs require intensive treatment immediately after diagnosis.

Staging. Staging is important in selecting a treatment and also for prognosis. CT scans of the neck, chest, abdomen, and pelvis, as well as bilateral bone marrow aspirate and

biopsy, are necessary to stage the lymphoma. Noncontiguous lymph node involvement, uncommon in Hodgkin disease, is more common among patients with NHL.

The Ann Arbor staging system is the most commonly used staging system for patients with NHL.

Stage I NHL involves a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II NHL involves 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ in addition to criteria for stage II (IIE).

Stage III involves lymph node regions on both sides of the diaphragm (III) that also may be accompanied by localized involvement of an extralymphatic organ or site (IIIE), spleen (IIIS), or both (IIISE).

Stage IV represents disseminated or multifocal involvement of one or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Subscript letters designate involvement of extralymphatic organs, as follows: L, lung; H, liver; P, pleura; O, bone; M, bone marrow; and D, skin. The designation E is used when extranodal lymphoid malignancies arise in tissues that are separate from but near the major lymphatic aggregates.

In this system, stages I-IV can be appended by A or B designations. Patients with A disease do not have systemic symptoms. The B designation is applied in patients with any of the following symptoms: unexplained loss of more than 10% of body weight in the preceding 6 months before diagnosis, unexplained fever with temperature above 38°C, and drenching night sweats.

In addition to staging, risk stratification is important in patients with NHL. Several scoring systems had been developed and validated prospectively in patients with diffuse large B-cell lymphoma (International Prognostic Index, IPI) or follicular B-cell lymphomas (Follicular Lymphoma International Prognostic Index, FLIPI) that can be used to predict the prognosis of patients with B-cell malignancies.

General treatment information

Once non-Hodgkin lymphoma has been diagnosed and staged, your cancer care team will discuss treatment options with you. Several different types of treatment can be used against non-Hodgkin lymphoma. The treatment options depend on the type of lymphoma and its stage (extent), as well as the other prognostic factors. Of course, no 2 patients are exactly alike, and standard options are often tailored to each patient's situation.

The main types of treatment for non-Hodgkin lymphoma are:

- Chemotherapy
- Immunotherapy
- Targeted therapy
- Radiation
- Stem cell transplant

In rare cases, surgery is also used.

Chemotherapy regimens:

R-CHOP	**Days 1, 22, and 43:** Rituximab 375mg/m^2 IV 7 days prior to beginning CHOP regimen **Day 1:** Cyclophosphamide 750mg/m^2 IV + doxorubicin 50mg/m^2 IV bolus + vincristine 1.4mg/m^2 IV bolus (max dose 2mg) **Days 3, 24, and 45:** Prednisone 100mg orally 5 days. Repeat each cycle every 3 weeks for 3 cycles. Radiotherapy begins 3 weeks after last cycle of R-CHOP.
Bendamustine ± rituximab	**Days 1–2:** Bendamustine 120mg/m^2 IV, **±** **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 28 days for up to 6 cycles.
Lenalidomide ± rituximab (non-GCB DLBCL)[42-44]	**Days 1–21:** Lenalidomide 20mg orally ± rituximab 375mg/m^2 IV weekly during cycle 1. Repeat every 28 days until complete response.
Patients >80 Years of Age With Comorbidities	
R-mini-CHOP[16]	**Day 1:** Rituximab 375mg/m^2 IV **Day 1:** Cyclophosphamide 400mg/m^{2}IV + doxorubicin 25mg/m^2 IV + vincristine 1mg IV **Days 1–5:** Prednisone 40mg/m^2 orally. Repeat every 3 weeks for 6 cycles.
Consolidation (optional)	
High-dose therapy with autologous stem cell rescue in patients with age-adjusted IPI high-risk disease (Category 2B)	Induced with 5 cycles of CHOP or R-CHOP **followed by** autotransplantation at the first response to induction therapy with CHOP with or without rituximab for 3 cycles.
High-dose therapy with autologous stem cell rescue in patients with double-hit DLBCL	Induced with 5 cycles of CHOP or R-CHOP followed by autotransplantation at the first response to induction therapy with CHOP with or without rituximab for 3 cycles.

Test evaluation and situational tasks.

Choose the correct answer/statement:

1. What disease is characterized by the high levels of plasma cells in the bone marrow?

A. Multiple myeloma
B. Chronic myelogenous leukemia
C. Idiopathic myelofibrosis
D. Polycythemia vera
E. Chronic hepatitis

2. Morphological diagnosis of Hodgkin's disease is characterized by the presence of the following cells in the lymph node histological preparations:
A. Reed–Berezovsky-Sternberg cells
B. Pirogov-Langans cells
C. Prolymphocytes
D. Lymphoblasts
E. Botkin cells

3. The most typical clinical syndrome for multiple myeloma is:
A. Anemic
B. Necrotic
C. Intoxication
D. Hemorrhagic
E. Infection

4. Which of the following are the most common complaints of patients with multiple myeloma?
A. Pain in the bones
B. Pain in the muscles
C. Asphyxia
D. Heartbeat
E. Sweating

5. The number of cells which greatly increased in the bone marrow in multiple myeloma?
A. Plasma
B. Blast
C. Cells Gaucher
D. Botkin cells
E. Megaloblasts

6. What changes in proteinogram are typical for multiple myeloma?
A. Hyperproteinemia with M-gradient
B. Hyperalbuminaemia
C. Hypoproteinaemia
D. Hypogammaglobulinemia
E. Hypergammaglobulinemia

7. Which of the following is typical for myelomic nephropathy?
A. Proteinuria
B. Oedema
C. Hypercholesterolemia
D. Leukocyturia
E. Pyuria

8. Which of these changes in the peripheral blood are typical for multiple myeloma?
A. Increased erythrocyte sedimentation rate and anemia
B. Leukemoid shift to the left
C. Leukocytosis
D. Thrombocytopenia
E. Blastosis

9. Which of the following are the most common complications of multiple myeloma?
A. Pathologic fractures
B. Gastrointestinal bleeding
C. Hemorrhagic syndrome
D. Thrombosis
E. Septic processes

10. Multiple myeloma - a malignant neoplasm of the hematopoietic system, which substrate are:
A. Plasma cells
B. Cell earliest predecessors of myelopoiesis
C. Pluripotent hematopoietic cells that are not able to mature
D. Mature B lymphocytes
E. Blasts

Real-life situations to be solved:

1. Patient 31 years old, went to the doctor complaining of enlarged lymph nodes above the clavicule on the left. During the physical examination: palpable enlarged painless lymph nodes on the left in the supraclavicular area. The liver and spleen are not enlarged. A blood test: hemoglobin - 120 g/l, leukocytes - $9.6*10^9$/L, 1 eosinophils 1%, bands - 5%, segments -70%, lymphocytes 18%, monocytes 6%, ESR -55 mm / h, PLT $58x10^9$/L. X-ray of the chest at the top of the right lung is determined the infiltration, which contrasts with the lung tissue. What test is needed to confirm the diagnosis? What is the most likely diagnosis?

2. The patient is 60 years old, male, complained of constant pain in the breasts and waist, which increases with the course, general weakness, shortness of breath. On radiographs wedge deformation of Th10, diffuse osteoporosis most vertebrae. In blood: HGB -94 g/l, RBC - $2,3\times10^{12}$/L, WBC - $2,7\times10^9$/l, PLT - $155,0\times 10^9$/L, ESR - 88 mm/h. Determined high level of M-protein in the blood serum. In urine protein - 3.2 g/L. In myelogram: the number of plasma cells – 19%.What is the most likely diagnosis?

Recommended literature:

I. Main:

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).

2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.
3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічнадіяліків – SideEffectsofMedications: навчальнийпосібнику 2 т. / зазаг.ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:
6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.
7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

II. Additional literature:

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
4. Principles and practice of interventional pulmonology / Ernst A., Herth F. - Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook fur medical students / Ye. Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143 .
7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook
9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook

11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)
17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).

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