Orzechowska Aleksandra, Widłak Karolina, Pawłowski Piotr, Ziętara Karolina, Orzechowska Julia. Plasma cell myeloma – therapeutic opportunities. Journal of Education, Health and Sport. 2022;12(8):18-27. eISSN 2391-8306. DOI https://dx.doi.org/10.12775/JEHS.2022.12.08.002
https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.08.002
https://zenodo.org/record/6584931

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Received: 02.05.2022. Revised: 15.05.2022. Accepted: 26.05.2022.

Plasma cell myeloma – therapeutic opportunities

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Absract

Introduction: Plasmocytic myeloma (PCM) is a neoplastic disease with a multistage course. Monoclonal plasmocytes undergo uncontrolled, multifocal growth in the bone marrow, which results in the production of monoclonal immunoglobulin or its fragments that damage the bone marrow.
Aim: The aim of this study is to present selected therapeutic possibilities of multiple myeloma.
Materials and methods: The work uses the method of non-systematic review and analysis of the available scientific literature. Databases such as PubMed, Google Scholar, Arianta, Scopus, Web of Science were searched. The years 2005-2022 were assumed as the review period.
Discussion: Multiple myeloma accounts for 1-2% of all cancer cases, and 10-15% of all hematological cancers. It is the third most common lymphoid neoplasm after chronic lymphocytic leukemia and large B-cell lymphoma. The diagnosis of PCM requires the presence of a minimum of 10% clonal plasmocytes in the bone marrow or biopsy confirmed plasmocytoma. Moreover, the CRAB and SLiM CRAB criteria are also important. Treatment should be initiated in all symptomatic patients meeting the SLiM CRAB criteria. The first stage of treatment is to induce remission of the disease.
Conclusions: Thanks to the progress of medicine, an increasing percentage of patients achieve permanent remissions. The success of the therapy is a component of the earliest possible detection of the disease and the use of appropriate, individually selected drugs.

Key words: Plasma cell myeloma; therapeutic opportunities; hematology; blood-borne tumors

Introduction

Plasmocytic myeloma (PCM) is a neoplastic disease with a multistage course. Monoclonal plasmocytes undergo uncontrolled, multifocal growth in the bone marrow, which results in the production of monoclonal immunoglobulin or its fragments that damage the bone marrow [Interna Szczeklika 2022, 1869-1927].

The development of PCM is a multi-stage process that probably always begins with an asymptomatic precancerous stage called monoclonal gammopathy of undetermined significance (MGUS). In some patients, in the process of evolution from MGUS to PCM, there is an additional, asymptomatic, intermediate stage called smoldering multiple myeloma (SMM) [Kumar S. et al., 2017].

Patients usually have a marrow infiltration of mature plasma cells, and a monoclonal protein is possible in the urine and/or serum.

Thanks to the progress of medicine, an increasing percentage of patients achieve permanent remissions, thanks to new drugs such as proteasome inhibitors or immunomodulating drugs. The success of the therapy is a component of the earliest possible detection of the disease and the use of appropriate, individually selected drugs [Iskierka-Jażdżewska E. et al., 2015, 245-263].

Aim

The aim of this study is to present selected therapeutic possibilities of multiple myeloma.

Materials and methods

The work uses the method of non-systematic review and analysis of the available scientific literature. Databases such as PubMed, Google Scholar, Arianta, Scopus, Web of Science were searched. The years 2005-2022 were assumed as the review period. Searches were carried out according to keywords in Polish and English, such as: plasma cell myeloma myeloma (PCM), multiple myeloma (MM), ASCT (Autologous stem cell transplantation), treatment, proteasome inhibitors, CAR-T.

The materials used in the work were scientific publications and academic textbooks in compact editorial offices. A review of the above-mentioned references provided information on the therapeutic possibilities of multiple myeloma.

Results

Epidemiology

Multiple myeloma accounts for 1-2% of all cancer cases, and 10-15% of all hematological cancers. It is the third most common lymphoid neoplasm after chronic lymphocytic leukemia and large B-cell lymphoma [Giannopoulos K. et al., 2018].

The incidence in Europe is 4.5-6/100,000 per year, and is more common in men. The peak incidence occurs in the 7th decade of life [Interna Szczeklika 2022, 1869-1927].

The risk factors for the disease include: the black race, where the risk occurs 2-3 times more often than among Caucasians. 90% of MM cases are diagnosed in people> 50 years of age, and only 2% of patients diagnosed with myeloma at diagnosis are under 40 years of age. Gender is also prognostic - about 1.5 times more often myeloma occurs in men [Jurszczyn A. et al., 2021].

MGUS and SMM

MGUS is found in 3% of the population above the age of 50, and its prevalence increases with age. The rate of progression from MGUS to MM is approximately 1% of patients per year. Some patients develop an intermediate disease stage between MGUS and MM, termed smoldering multiple myeloma SMM [Van Nieuwenhuijzen N. et al., 2018, 2449–2456].

MGUS criteria:

- serum monoclonal protein <30 g/L;
- clonal BM plasma cells (PCs) <10%; and
- absence of end-organ damage (hypercalcemia, renal insufficiency, anemia, and bone lesions) [Maciocia N. et al., 2016].

Smoldering multiple myeloma (SMM) represents a transitional stage between monoclonal gammopathy of undetermined significance (MGUS) and active multiple myeloma (MM). The standard of care for SMM, irrespective of the risk status of the patients, has been observation.

María-Victoria Mateos et al. have done a study to show the benefits of early treatment in reducing the risk of progressing to MM. The study compared the effect of lenalomide with dexamethasone, which showed that lenalidomide significantly delayed the progression to MM and that patients lived longer [Mateos MV et al., 2020].

Diagnostics

The diagnosis of PCM requires the presence of a minimum of 10% clonal plasmocytes in the bone marrow or biopsy confirmed plasmocytoma [Rajkumar SV, 2020, 548-567].

Moreover, the CRAB (MM- Multiple Myeloma) criteria are also important, including:
- C (Calcium - hypercalcemia) - corrected serum calcium concentration> 0.25 mmol / L above the upper limit of the reference value or> 2.75 mmol / L,
- R (Renal insufficiency), - serum creatinine concentration> 2 mg / dl or creatinine clearance,
- A (anemia - anemia) - hemoglobin concentration 2g / dl below the lower reference value or below 10g / dl,
- B (bones - changes in bones) - one or more osteolytic lesions in a classic radiological examination, computed tomography (CT) or positron emission tomography (PET-CT),
and SLiM CRAB (SMM- Smoldering Multiple Myeloma), the diagnosis of which is based on the following criteria:
- S (Sixty - 60) - the percentage of clonal plasmocytes in the bone marrow or tissue biopsy is at least 60%,
- Li (Light Chains - light chains) - serum concentration ratio of clonal to non-clonal free light chains is at least 100, with the concentration of the clonal chain in the serum should be at least 100 mg / dl,
- M (Magnetic Resonanse - magnetic resonance examination) - presence of min. two focal infiltrates in the Whole Body STIR examination, at least 5 mm each [Giannopoulos K. et al., 2018].

Treatment

The choice of the appropriate treatment method for the patient should be based on the assessment of the patient's general fitness and the presence of comorbidities. The potential toxicity of specific therapies should also be taken into account.

First-line treatment and sequential treatment

Treatment should be initiated in all symptomatic patients meeting the SLiM CRAB criteria. The first stage of treatment is to induce remission of the disease, taking into account the patient's age. Patients under the age of 70 without aggravating comorbidities are eligible for High Dose Therapy (HDT) assisted by auto-Hematopoietic Stem Cell Transplantation (autoHSCT).
For patients who are not eligible for autoHSCT, low-dose melphalan treatment is used in combination with other newer drugs. These include: bortezomib, thalidomide, lenalidomide [Giannopoulos K. et al., 2021].

Francesca Gay et al. in their study evaluated a sequential approach involving bortezomib induction, intermediate dose melphalan and autologous stem cell transplant (ASCT), followed by lenalidomide consolidation treatment and maintenance therapy. Patients with diagnosed myeloma aged 65-75 years participated in the study. They received 4 cycles of bortezomib-pegylated liposomal doxorubicin-dexamethasone, tandem melphalan (100 mg/m2) followed by ASCT (MEL100-ASCT), 4 cycles of lenalidomide-prednisone consolidation (LP), and lenalidomide maintenance (L) until disease progression.

The following results were obtained:

- the complete response (CR) rate was 33% after MEL100-ASCT, 48% after LP and 53% after L maintenance,
- in CR patients, median TTP (time-to-progression) was 70 months,
- median survival from relapse was 28 months,
- rate of death was higher among patients under the age of 70.

Therefore, the greatest benefits are achieved by patients up to 70 years of age who have been used bortezomib-induction followed by ASCT and lenalidomide consolidation treatment [Gay F. et. al., 2013, 1376-1383].

CAR-T therapy

T-cell therapy works differently from other therapies that are used to MM. It uses chimeric antigen receptors (CAR) and involves the modification of patient or donor T cells to target specific cell-surface antigens. B cell maturation antigen (BCMA) is expressed only on plasma cells, a small subset of B cells and MM cells, which makes it a perfect target antygen [Mikkilineni L. et al., 2021, 71-84].

Toxicities associated with CAR T cells include cytokine-release syndrome, different types of cytopenia, infections, and neurotoxicity. Although some subsets of patients have sustained responses for more than 1 year, most patients eventually relapse, which might be related to the loss of CAR T cells, loss of antigen expression on the tumour cell surface, or to an immunosuppressive microenvironment that impairs the activity of T cells [Van de Donk NWCJ et al., 2021, 446-461].

CAR-T cells can recognize cell surface molecules and it is possible without the help of HLA expression. It is an advantage because the tumors often avoid T cell immune surveillance by hiding HLA or other molecules that may be helpful in antigen processing and presentation [Zhao Z. et al., 2018, 539-551].

Proteasome inhibitors

Ixazomib is a new registered cure for adult patients with plasma cell myeloma who have been treated with at least one therapy. It is the first oral proteasome inhibitor and it used in in combination with lenalidomide and dexamethasone.

Ixazomib binds preferentially and reversibly to the beta 5 subunit with chymotrypsin-like activity in the 20S proteasome. It induces apoptosis of the cancer cells. ixazomib has also been shown to be cytotoxic to myeloma cells in patients who have relapsed after previous drug use [Giannopoulos K. et al., 2017, 160-164].

The other of proteasome inhibitors- Bortezomib also induces apoptosis of the multiple myeloma cells that makes them sensitive for chemotherapy. What is more, it blocks cytokine circuits, cell adhesion, and angiogenesis.

Bortezomib is a modified dipeptidylboronic acid, chich binds selectively and reversibly to the proteasome and inhibits chymotrypsin-like effectsin the β-ring of the 26S proteasome.

Traditional drugs which are used in chemotherapy not only of plasma cell myeloma have better opportunities to work because cells are more sensitive for chemotherapy because of Bortezomib. Ihibition of proteasome increases sensitivity for radiotherapy [Warzocha K. et al., 2007, 160-169].

Marizomib is an irreversible proteasome inhibitor which is under investigation in relapsed-refractory multiple myeloma (RRMM). Extra-medullary relapse, especially central nervous system (CNS) involvement continues to confer poor prognosis. There are neoplastic plasma cells in the cerebrospinal fluid (CSF) and in meninges. Several studies showed that marizomib localizes to the CNS and its action inhibits proteasome activity in the brain.

The use of marizomib causes clinical improvement in neurological symptoms and reduction of plasmocytes in CSF [Badros A. et al., 2017, 221-225].

Oprozomib is an oral, selective and irreversible epoxyketone proteasome inhibitor. In RRMM patients, oprozomib demonstrated promising efficacy when used as a single-agent or in combination therapy [Hari P. et al., 2019].

Autologous stem cell transplantation (ASCT)

Transplantation of allogeneic hematopoietic cells remains the only treatment option. This option should be considered especially in young patients at high risk.

The main advantage of this method is the possibility of using myeloablative doses of chemotherapy or radiation (conditioning), without the risk of tumor cell retransplantation.

Moreover, alloreactive T lymphocytes are present in the transplant material, the main function of which is to eliminate the remaining myeloma cells from the recipient's body.
Unfortunately, this procedure has a very high risk of complications. There are mainly infectious complications resulting from a long state of immunosuppression and the occurrence of a "graft-versus-host" disease [Giebel S., 2018, 245-247].

An important element of the transplant procedure is the type of conditioning regimen. A dose of 200 mg / m2 of melphalan is administered. It is assumed that after 65 years of age the dose of melphalan in conditioning should be reduced to 100-140 mg/m^2, but current studies indicate that maintaining the dose of 200 mg/m^2 did not increase mortality in patients over 65 years of age.
Recently, attempts have been made to add busulfan to melphalan, but so far it has not been shown that such a combination results in better results than using only high doses of melphalan [Cioch M., 2019, 130-134].

Thalidomide monotherapy or in combination with dexamethasone

According to the study described by Hanna Ciepłuch et al. on the use of thalidomide in patients with refractory or relapsed multiple myeloma, this drug is effective in 30-50% of patients. sick. Even cases of complete remission have been described. Thalidomide has, inter alia, an immunomodulatory effect on the secretion of cytokines (inhibition of IL6, TNF, IL1β, induction of IL2, IFγ), reduction of VEGF and increased expression of adhesion molecules on myeloma plasmocytes. It is a drug whose effectiveness has been proven in the treatment of multiple myeloma, also in patients who have relapsed after high-dose chemotherapy.
In the case of dexamethasone, proliferation is inhibited and the apoptosis of myeloma cells is induced. The production of IL6 is blocked and the expression of the IL6 receptor on myeloma cells is inhibited. Ultimately, the use of these two drugs enhances the neutralizing effect of IL6. The mechanisms of action of these drugs are independent, but the combination of dexamethasone with thalidomide increases their anti-proliferative effect in the case of IL6 [Ciepłuch H. et al., 2003, 273-277].

Conclusions

Multiple myeloma is a neoplastic disease with a multi-stage course. The development of PCM is a multi-stage process that probably always begins with an asymptomatic precancerous stage called monoclonal gammopathy of undetermined significance (MGUS). In

some patients, in the process of evolution from MGUS to PCM, there is an additional, asymptomatic, intermediate stage called smoldering multiple myeloma (SMM).

Patients usually have a marrow infiltration of mature plasma cells, and a monoclonal protein is possible in the urine and / or serum. Multiple myeloma accounts for 1-2% of all cancer cases, and 10-15% of all hematological cancers.

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Treatment should be initiated in all symptomatic patients meeting the SLiM CRAB criteria. The first stage of treatment is to induce remission of the disease. The choice of the appropriate treatment method for the patient should be based on the assessment of the patient's general fitness and the presence of comorbidities. Patients under the age of 70 without aggravating comorbidities are eligible for High Dose Therapy (HDT) assisted by auto-Hematopoietic Stem Cell Transplantation (autoHSCT).

For patients who are not eligible for autoHSCT, low-dose melphalan treatment is used in combination with other newer drugs. These include: bortezomib, thalidomide, lenalidomide. CAR-T therapy is also used. It uses chimeric antigen receptors (CAR) and involves the modification of patient or donor T cells to target specific cell-surface antigens.

Very good results are also observed with the use of drugs from the proteasome inhibitors group. However, it is the transplantation of allogeneic hematopoietic cells that remains the only method that offers a chance of a cure. This option should be considered especially in young patients at high risk.

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