ejpmr, 2020,7(9), 48-55

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

REVIEW ON THE METRONOMIC THERAPY OF MULTIPLE MYELOMA

Iftikhar Ali[1], Mati Ullah[2], Shahzad Gul Hasan[3] and Shangqin Liu[*4]

[1]Department of Hematology, Zhongnan Hospital, Wuhan University, Wuhan, China.
[2]Department of Biotechnology, College of Life Science and Technology, Huazhong University of Science and Technology, 1037 Luoyu Road, Wuhan 430074, China.
[3]Department of Cardiovascular Diseases, Renmin Hospital Wuhan, Wuhan University, Wuchang District, Wuhan 430072, China.
[4*]Department of Hematology, Zhongnan Hospital of Wuhan University, 169, East Lake Road, Wuchang District, Wuhan 430071, China.

***Corresponding Author: Shangqin Liu**

Department of Hematology, Zhongnan Hospital of Wuhan University, 169, East Lake Road, Wuchang District, Wuhan 430071, China.

Article Received on 07/07/2020 **Article Revised on 28/07/2020** **Article Accepted on 17/08/2020**

ABSTRACT

Metronomic chemotherapy is a new method of administrating drug that overcomes the hurdles faced by conventional therapy. This multidrug regimen involves the administration of comparatively low but frequent doses of conventional chemotherapeutic drugs with break free intervals to prevent relapse or resistance. The target tissue of metronomic therapy is activated endothelial cells of the blood vessels as opposed to conventional therapy. Conventional chemotherapy is the previous treatment modality which involves Maximum Tolerated Dose (MTD) with intervals. The rest periods between the therapies was made to avoid any drug toxicity and to reduce the side effects faced by the patients. However, this led to the re-growth of the tumor cells and chemo resistance. In this article, we will evaluate the benefits of metronomic chemotherapy for patients suffering from multiple myeloma. With the knowledge of the previous therapeutic protocols against cancer, we will discuss the new modality in detail to figure out the clinical benefits of this treatment.

KEYWORDS: Metronomic chemotherapy, conventional chemotherapy, angiogenesis, malignant cells, toxicity, Multiple myeloma, plasma cells, cancer.

BACKGROUND

Cancer is the development of the uncontrolled growth of immature cells anywhere in the body. These abnormal cells have the potential to infiltrate and spread to other parts of the body, thus called malignant.[1] Multiple Myeloma also called Kahler's disease is a blood cancer of plasma cells.[2] Plasma cells are short-lived, immunoglobin producing cells that originate in the bone marrow. They are found in the bloodstream, lymph nodes, intestines, and bone marrow.[3] These cells are very important for the body's system of immunity to fight off infection and to kill bacteria. When the third line of the defense mechanism of the immune system fails to provide a barrier against invading microorganisms, B and T lymphocytes come into action.[2] These specific immune cells provide an adaptive immune response against pathogenic invasions and antigens. During infection, the B lymphocytes secretes the specific antibiotics upon the maturation. These plasma cells are differentiated B-lymphocytes that produce specific antibodies to kill bacteria. These lymphocytes also mature and produce memory cells to protect the body for future invasions.[4]

In Multiple Myeloma, abnormal plasma cells proliferate in the spongy material present in the center of the long bones, the bone marrow.[5] The uncontrolled growth and accumulation of the malignant plasma cells outgrow the normal healthy plasma cells, thus declining the body's ability to fight off infections. These monoclonal plasma cells synthesize proteins (antigens) that provide no defense mechanism to the body and are of no benefit. Nevertheless, they have many negative effects and can cause tumors, malfunctioning of kidney, destruction of bones and the impaired immune response.[2]

With the advance in technology, cancer search is also progressing. Conventional chemotherapy and other treatments have more cons than pros. The treatment strategy of conventional chemotherapy do not provide much benefits. It has many adverse effects and it does not provide a cure for the malignancies. All these drawbacks have led scientists to explore new therapeutic strategies to treat cancer patients. Thus, scientist shifted their target from anti-cancer drugs to anti-angiogenesis drugs. The angiogenesis inhibitor drugs came into establishment but it did not turn out to be a very

beneficial drug. It only increased life expectancy to a few months, not more.[6,7]

Later, it came into notice that the conventional chemotherapeutic drug has an anti-angiogenetic effect when administered in a low dose. This lead to the concept of treating cancer patients with metronomic chemotherapy. Hence we can define metronomic chemotherapy as "frequent administration of multidrug at low dose without break fee intervals". Previous studies suggested that these drugs target on the activated endothelial cells. This target switch that is anti-angiogenic property of the metronomic therapy was considered its main line of action. But later, additional mechanisms of this multidrug regimen came into lightening. The discovery of these additional mechanisms of the metronomic chemotherapy has established it as multi-targeted therapy.[8,9]

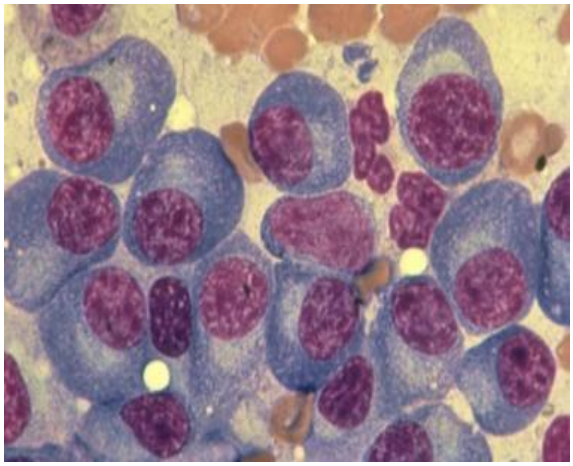


Figure 1: Plasma cells of multiple myeloma.

CAUSES OF MULTIPLE MYELOMA

The main cause of multiple myeloma is still unknown, not identified yet, although scientists have pointed out certain risk factors that may play a role in its cause. The most important of which is genetic abnormalities.[10] The c-Myc genes are involved in the genetic mutation. Many scientists do not consider Multiple Myeloma to be a hereditary disease.[11] Yet, some familial history in patients with Multiple Myeloma has been found. There is a close link between the Multiple Myeloma and MGUS. One in every 100 patients of MGUS develops Multiple Myeloma. Some factors may accelerate the risk of Multiple Myeloma. The disease is more common in male individuals, old people and adults over 60. Widely it affects African and American, while it is twice more common in blacks than Asian whites along with family history of Multiple Myeloma or MGUS.[8]

TREATMENT OF MULTIPLE MYELOMA

Proper cure for this disease has not discovered yet. However, treatments can help relieve the symptoms. It helps to control the disease and its complication, prolong life expectancy, and provide a healthy lifestyle for years.[12] Treatment of Multiple Myeloma includes Chemotherapy i.e. Metronomic Chemotherapy (MC) along with medicines and general treatment of other problems caused my Multiple Myeloma; such as bone destruction and fracture, anemia, and impaired kidney problem. Targeted therapy involves medications that destroys proteins in the malignant cells, thus causing it to die. Biological therapy involves medications that's uses the immune system of the body to attack the tumor cells. Thalidomide (Thalomid), lenalidomide (Revlimid), or pomalidomide (Pomalyst) are the medicines given to enhance the immune system.[13,14]

Corticosteroids; such as dexamethasone or prednisone reduces the inflammation in the body. They can be used to treat Multiple Myeloid as they help in destroying the malignant plasma cells [2]. Stem cell transplants; by replacing diseased spongy bone marrow with healthy bone marrow from a donor, is done along with chemotherapy. It uses high doses regimen of chemotherapy along with Autologous Stem Cell Transplant (ASCT) to kill the malignant stem cells.[15]

CONVENTIONAL CHEMOTHERAPY

Chemotherapy is an aggressive form of drug therapy that uses powerful chemicals to destroy rapidly dividing cells.[16] They are used for both local and malignant neoplasms. However, the treatment is accompanied by short and long term side effects and reactions. The collateral damage with the cyclic use of chemotherapy can limit its dose and anti-tumor efficacy.[17] This intensive drug treatment uses high doses regimen along with Autologous Stem Cell Transplant (ASCT) to kill the malignant stem cells. All this weakens the immune system and requires proper medical care and attention.[18] Conventional chemotherapy uses Maximum Tolerable Dose (MTP) to kill and eliminate the malignant cells. The drug-free interval is prolonged to help the patient recover from the side effects of the drug. One of the major drawbacks of this treatment is that during the drug-free interval, relapse or reoccurrence can occur Also, the malignant cells can develop resistance to the chemotherapeutic drug. This further complicates the plan of treatment and is a huge setback for both, the doctor and the patient.[19]

NEW LINE OF TREATMENT

With the advance in technology, scientists discovered a new fact about the tumor growth and metastasis which is related to the growth of new blood vessels. The concept is based on the fact that by using anti-angiogenesis drugs, the tumor cells can be starved to death (. Without the formation of new blood vessels, the neoplasia would not able to nourish itself with nutrients, thus stopping its growth and spread. Thus, scientist shifted their target from anti-cancer drugs to anti-angiogenesis drugs. The angiogenesis inhibitor drugs came into establishment but it did not turn out to be a very beneficial drug. It only increased life expectancy to a few months, not more.[20] Later, it came into notice that the conventional chemotherapeutic drug has an anti-angiogenetic effect

when administered at a low dose. This lead to the concept of treating cancer patients with metronomic chemotherapy.[19]

METRONOMIC CHEMOTHERAPY

The main approach of metronomic chemotherapy was first revealed by the Hanahan. The term Metronomic Chemotherapy is currently used to describe the regular administration of chemotherapeutic agents at a very low doses but for a longer period of time. It is a new method of administrating drug that overcomes the hurdles faced by conventional therapy. This multidrug regimen involves frequent administration of low doses of conventional chemotherapeutic drugs with break free intervals to prevent relapse or.[21,22] The important characteristics features of Metronomic Chemotherapy are: a) Direct inhibition of tumor growth; direct cytotoxic activity to tumor cells (cancer stem cells), b) Inhibition of vasculogenesis and angiogenesis, c) Activation of immunity, d) No application of Hematopoietic Growth factor, e) Low dose without break free interval, f) Preference for oral drugs, g) No chemoresistance, and h) No injurious side effects. However, the use of metronomic chemotherapy in the clinical setup has been limited palliative purposes in relapse/refractory diseases and metastatic cases. The metronomic chemotherapy can be used for maintenance strategy. It can also be performed as a assiduity of the induction regimen in which case one or two drugs already used in the induction regimen are carried out as maintenance.[21] Metronomic chemotherapy can also be used as a switch maintenance therapy. In this case, a short period of conventional chemotherapy is carried on which is later followed by the extended courses of non-cross-resistant cytotoxic drugs.[23,24]

MECHANISM OF ACTION OF METRONOMIC CHEMOTHERAPY

The interaction of the tumor and its surroundings like its microenvironment have led scientist to hypothesize a new mechanism of action of chemotherapeutic drugs to provide anti-cancer activity. Metronomic Chemotherapy is a multitargeted therapy which has both direct and indirect effect on the malignant tumor cells and its microenvironment.[25] A high dose of chemotherapy should not be considered anti-angiogenic. Dose above MTD causes endothelial toxicity and is not considered safe. The mechanism of action of chemotherapy consists of its anti-angiogenic property, activation of immunity, tumor dormancy induction, and 4D effect.[26]

Anti-angiogenic Properties

Metronomic chemotherapy inhibits angiogenesis by direct killing or inhibition of the endothelial cells.[27] This anti-cancer property of metronomic therapy is carried out by: a) Inhibition of activated endothelial cells apoptosis, b) Inhibiting the selective migration of endothelial cells, c) Up regulation of thrombospondin-1 which is an endogenous inhibitor of angiogenesis, and d) Inhibition of ECP (endothelial progenitor cells.[26]

Activation of immunity

The new approach of Metronomic Therapy turns out to be very useful. Some scientists have suggested that the suppression in immune system caused by chemotherapy can lead to tumor cell growth. This is due to neutropenia and lymphopenia of White Blood Cells.[26] However, new researches have proposed that while some cytotoxic drugs like Anthracyclines, taxanes, cyclophosphamide suppress part of the immune system, some WBC like T cells (Natural killer cells) help in sustaining immune-stimulatory properties. These regulatory T cells (T_{reg}) are $CD4^+$ $CD25^+$. By inhibiting anti-tumor immune response, antigen specif. Thus suppressing the activity of both, tumor-specific and tumor-unspecific effector cells. Tumor-specific cells are $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T helper cells. Natural killer (NK) and NK T cells are those unspecific effector cells which increase T_{reg} cells in the body mean that the tumor is progressing and is somewhat ineffective to the treatment provided.[28]

Induction of tumor dormancy

Tumor cells are not active during the early of tumor formation, which is before the vascular phase. This is called tumor dormancy. Some scientists suggest that this phase comes after the completion of the chemotherapy, which is during the remission phase. Suppression of blood vessel formation, programmed cell death of malignant cells, and immune-surveillance are three main methods by which metronomic chemotherapy induces tumor dormancy. In tumor mass dormancy, there is stagnation of the tumor cell proliferation because of the dynamic equilibrium state. This phenomenon can be observed during the early stage as well as after the therapy in the remission phase.[29]

Induction of senescence

Chemotherapeutic agents *can* cause low-grade damage. This initiates senescence associated with anti-proliferative response. The cascades of caspase activity that induce cellular apoptosis are not activated. The induction of senescence in tumors can be done by repetitive, low-dose regimens of cytostatic drugs.[30]

Four-Dimensional effects

Cell dependency which is followed by the sudden withdrawal or subsequent drug deprivation due to the chemotherapy is called the 4D effect. It has been postulated that the therapeutic effect of metronomic therapy is not only because of the anti-angiogenic and immune-stimulatory effect of the drug but also due to the direct anti-cancer activity. Because of the long exposures of chemotherapeutic agents, tumor cells become dependent on these drugs. So, the sudden withdrawal of the drug can lead to the death of the tumor cells. This explains why multiple drugs are used with a differing period of administration.[25]

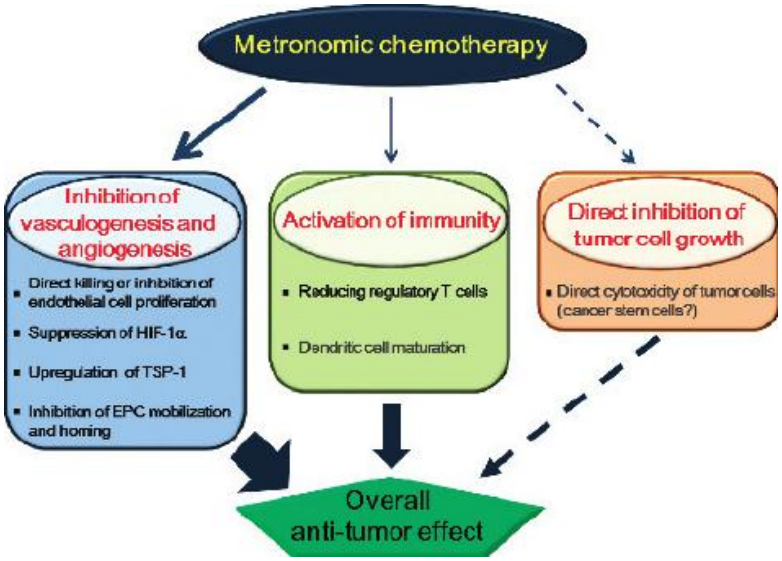


Figure 2: Mechanism of action of metronomic chemotherapy.

Table 1: Differences between conventional and metronomic chemotherapy.

Conventional chemotherapy	**Metronomic chemotherapy**
Used at their Maximum Tolerance Dose (MTD)	Used at low dose
Targets tumor cell	Targets endothelial cells of blood vessels
After its administration, the plasma concentration of the dug gradually rises and then falls	Concentration of the drug is sustained in the plasma
Given at regular intervals	Dosing frequency is continuous such as daily or weekly
Administered with the purpose to treat cancer by directly inhibiting or killing the abnormal tumor cells	Inhibition of vasculogenesis or angiogenesis is the main target
No significant adverse effect or chemo resistance, also there is a reduced need for medical support	Side effects and toxicity are of major concern

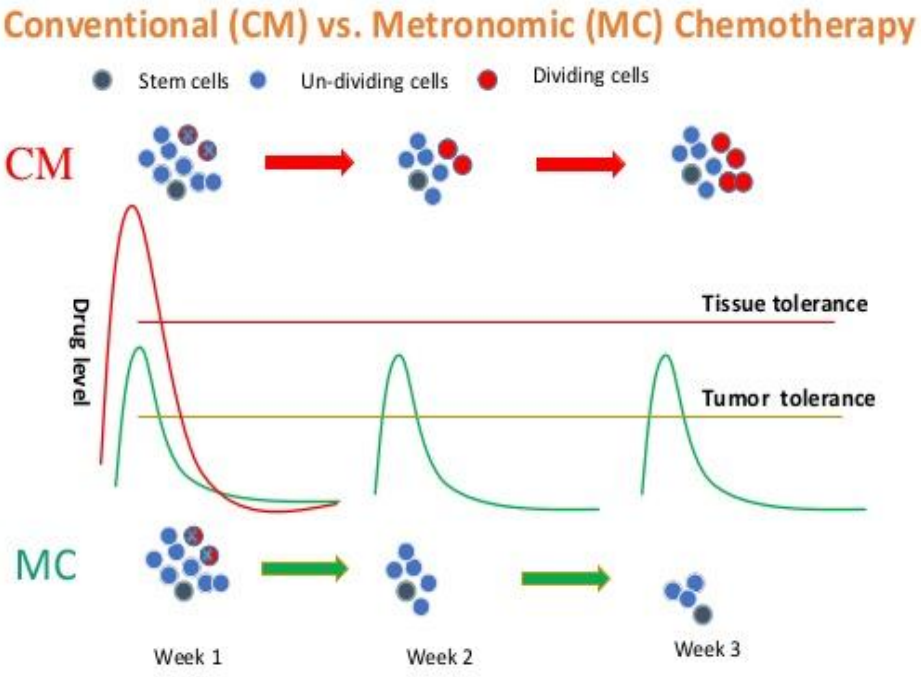
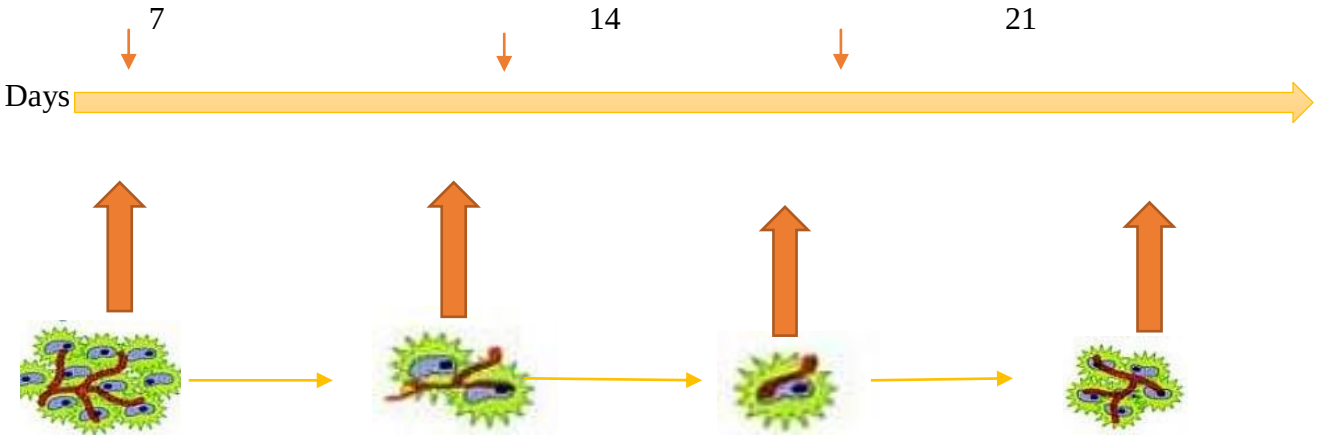


Figure 3: Conventional VS Metronomic chemotherapy.

Conventional chemotherapy

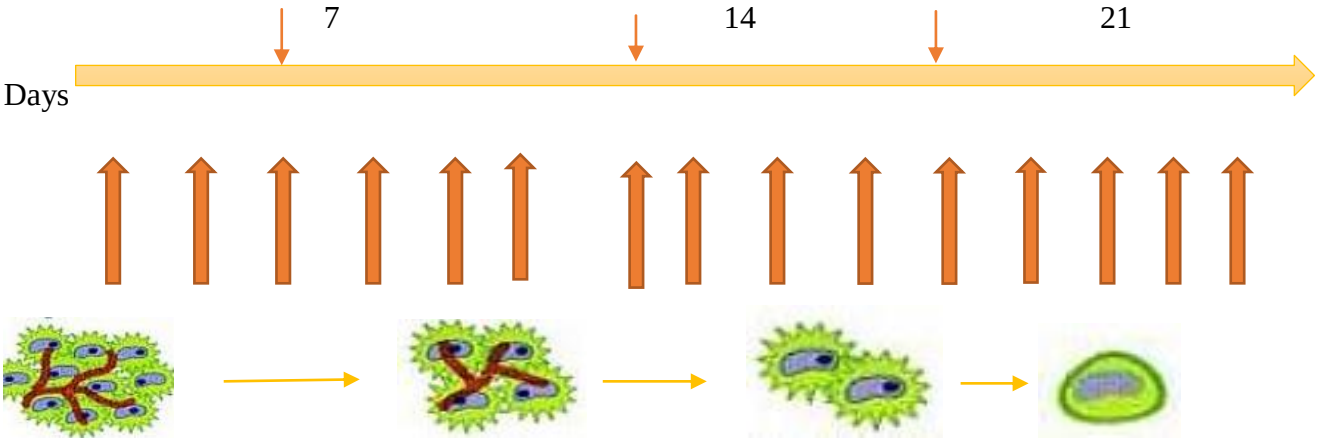
(Administrates intermittently)



Initial tumor Tumor after first treatment Tumor after 2nd treatment Recurrence

Metronomic chemotherapy

(Administrates Continuously)



Initial tumor Tumor at 14 days Tumor after 21 days Remission

METRONOMIC THERAPY OF MULTIPLE MYELOMA

The main goal of metronomic therapy is to reduce or eliminate the growth and spread of the tumor, to provide a hostile environment for the tumor cells, to prevent relapse or recurrence, and to help the body and it's immune system to fight off infection and recover its health and potential.[12] Low dose metronomic chemotherapy is cytotoxic to tumor cells of Multiple Myeloma buy is non-toxic for other healthy cells of the human body.[31] The new drug has many benefits that can improve treatment modalities in cancer patients. This emerging treatment of cancer is based on the concept of reducing the dose and increasing the frequency of the chemotherapeutic drug. Hence, leading to a dramatically slow and stable tumor for a long term but not necessarily targeting the complete elimination of the malignant cells.[32]

The multidrug regimen use in metronomic chemotherapy has provided better treatment options for patients that were refractory to all other treatment modalities. Because of the low dose and reduce side effects, this drug has turned out quite beneficial for patients with Multiple Myeloma.[33] The repetitive low dose with high frequency has enabled the drug to treat patients of Multiple Myeloma without causing any adverse side effects or toxicity.[5] The results turned out quite beneficial for both, the doctors and the patients. This multidrug regimen is fairly well tolerated in patients with multiple myeloma.

DRUGS USED IN METRONOMIC THERAPY

Metronomic chemotherapy is a multidrug therapy which includes drugs of various classes that have anti-angiogenic, apoptotic, and immune-stimulatory properties.[34,35] Some anti-cancer drugs, when given at break free intervals in low doses, can cause damage to both, circulating endothelial cells and circulating CEPs.[36] Whereas it has no effect on white blood cells and non-endothelial cells. These anti-cancer drugs include CPA, methotrexate, etoposide, vinblastine, paclitaxel. Endothelial cells are genetically stable so even with a high dose of chemotherapy, they are less suspectable to develop resistance. Whereas tumor cells can develop resistance if administered with cyclic breaks and intervals. Thus, endothelial progenitor cells may help as a surrogate biomarker to determine the Optimum Biological Dose of metronomic chemotherapy regimens.[22]

Scientists have observed that when resistance has developed to the Maximum Tolerated Dose of conventional therapy, treatment modality is no longer effective. Thus, switching over to metronomic chemotherapy at such circumstances has proved quite beneficial. Metronomic doses are around one-tenth of the Maximum Tolerated Dose (MTD) of conventional chemotherapy. Hence, toxicity is not a concern. Therefore the aim of phase one clinical trial is to obtain the Optimum Biological Dose (OBD) of a drug.[37,38]

PRECLINICAL AND CLINICAL DATA

In preclinical evaluation, the most frequently used drug was Cyclophosphamide. By combining cyclophosphamide with methotrexate, UFT, and vinorelbine, long term survival effects were observed. Research has demonstrated that methotrexate and vinorelbine, when given in a metronomic way, can retrogress cancer resistance. Whereas when the same drugs are administered conventionally, it can increase the tumor volume rapidly after two to three weeks. Another researcher pointed out that the growth of the endothelial cells of the blood vessels and its microenvironment can be influenced by the dose regimen of metronomic chemotherapy. At a concentration of $5 \times 10{-}9$ M, methotrexate inhibits cell proliferation. At a dose of 10 pM, paclitaxel downregulates chemo toxins. Docetaxel is ten times more effective than paclitaxel when given at a low dose. It inhibits cell migration and capillary sprouting. At an ultra-low concentration of 0.1-1 pM, vinblastine inhibits proliferation of human endothelial cells, migration, and metalloproteinase secretion. Other researchers are still working and investigating preclinical designs to evaluate the impact of the low dose of metronomic chemotherapy on the cancer cells and its microenvironment.[19,35]

Total of 18 drugs were used as a single drug and in combinations. The most commonly employed drugs were cyclophosphamide, methotrexate, capecitabine, bevacizumab, and vinorelbine. Cyclophosphamide and methotrexate were administered in doses of 50mg once daily and 2.5mg twice daily respectively. From the clinical side, mixed results have been obtained. Drugs such as Vinorelbine, cyclophosphamide, capecitabine, methotrexate, and bevacizumab have been tested. Different combinations of these various drugs have proved beneficial with the treatment of different carcinomas.[35,39]

TOXIC EFFECTS OF METRONOMIC DRUGS

The preclinical and clinical trials have highlighted the fact that these metronomic drugs are not devoid of side effects. These drugs are generally well tolerated by the patients as compared to conventional chemotherapy. However, some drawbacks and treatment interruptions were noted. So it must be kept in mind to avoid all these drawbacks which occurs due to the treatment for a longer time. The most common side effects of treatment with metronomic chemotherapy includes: Nausea and vomiting (Grade 1), anemia (Grade 2 and 3), low concentration of neutrophils, low concentration of leukocytes (white blood cells), low concentration of lymphocytes (B and T lymphocytes) and low-grade fatigue. Cumulative effects can lead to secondary leukemia, or myelodysplastic syndrome (MDS).[40,41] Vinorelbine, cyclophosphamide, capecitabine, and methotrexate are some of the main drugs in which these severe effects can be seen. These toxic effects are more concerning and frequent when administered in combination. It is important to note that these metronomic therapeutic drugs are really toxic with the addition of bevacizumab (modern effective drug). Some studies have shown hypertension, excess protein in the urine, and kidney failure as an adverse effect to the metronomic chemotherapy. Taking into consideration that when a modern targeted drug is added to the metronomic chemotherapy, it can cause gastrointestinal problems such as diarrhea, nausea, vomiting as well as fatigue.[38]

CONCLUSION

The ideal treatment of chemotherapy is to eliminate malignant cells and to provide complete tumor suppression. The previous treatment modalities did provide tumor remission with its Maximum Tolerated Dose (MTD). But it was usually followed by re-growth, reoccurrence, and resistance of the tumor cells which are

even more malignant than the previous one. With recent studies and researches, scientists have changed their angle of thinking. Instead of coming up with a magic drug that would destroy the malignant cell, they came up with a multi-therapeutic drug therapy that has an effect on both, the cancer cells and its microenvironment. This treatment modality is called metronomic chemotherapy. The multidrug regimen use in metronomic chemotherapy has provided better treatment options for patients that were refractory to all other treatment modalities. Because of the low dose and reduce side effects, this drug has turned out quite beneficial for patients with Multiple Myeloma. The positive outcome has led to the concept of treating patients of Multiple Myeloma with metronomic chemotherapy.

REFERENCES

1. Rajkumar SV. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematol*, 2018; 93(8): 1091-1110.
2. Kim S, Son E, Lee S, et al. Multiple myeloma associated with IgA lambda gammopathy and multiple myeloma oncogene 1 in a Yorkshire terrier. *Vet Med (Praha)*, 2018; 63(4): 187-192.
3. Vangsted A, Klausen TW, Vogel U. Genetic variations in multiple myeloma II: association with effect of treatment. *Eur J Haematol*, 2012; 88(2): 93-117.
4. Li L, Wang L. Multiple myeloma: what do we do about immunodeficiency? *J Cancer*. 2019; 10(7): 1675.
5. Kim HJ, Kwon J, Jung JY, Yoon SS. Metronomic chemotherapy of thalidomide, cyclophosphamide, and dexamethasone for relapsed/refractory multiple myeloma patients. *Clin Lymphoma, Myeloma Leuk*, 2015; 15: e311-e312.
6. Nijhof IS, van de Donk NWCJ, Zweegman S, Lokhorst HM. Current and new therapeutic strategies for relapsed and refractory multiple myeloma: an update. *Drugs*, 2018; 78(1): 19-37.
7. Kumar S, Gertz MA, Dispenzieri A, et al. Prognostic value of bone marrow angiogenesis in patients with multiple myeloma undergoing high-dose therapy. *Bone Marrow Transplant*, 2004; 34(3): 235-239.
8. Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: new rationale for new directions. *Nat Rev Clin Oncol*, 2010; 7(8): 455.
9. Gnoni A, Silvestris N, Licchetta A, et al. Metronomic chemotherapy from rationale to clinical studies: a dream or reality? *Crit Rev Oncol Hematol*, 2015; 95(1): 46-61.
10. Koltai T, Cardone RA, Reshkin SJ. Synergy Between Low Dose Metronomic Chemotherapy and the pH-Centered Approach Against Cancer. *Int J Mol Sci*, 2019; 20(21): 5438.
11. Goldschmidt H. Can we cure Multiple Myeloma by 2020? No. *Clin Lymphoma, Myeloma Leuk*. 2015; 15: e36-e37.
12. Bergin K, McQuilten Z, Moore E, Wood E, Spencer A. Myeloma in the real world: what is really happening? *Clin Lymphoma Myeloma Leuk*, 2017; 17(3): 133-144.
13. Pönisch W, Rozanski M, Goldschmidt H, et al. Combined bendamustine, prednisolone and thalidomide for refractory or relapsed multiple myeloma after autologous stem-cell transplantation or conventional chemotherapy: results of a Phase I clinical trial. *Br J Haematol*, 2008; 143(2): 191-200.
14. Podar K, Tai Y-T, Hideshima T, Vallet S, Richardson PG, Anderson KC. Emerging therapies for multiple myeloma. *Expert Opin Emerg Drugs*, 2009; 14(1): 99-127. doi:10.1517/14728210802676278.
15. Bird SA, Boyd K. Multiple myeloma: an overview of management. *Palliat Care Soc Pract*. 2019; 13: 1178224219868235.
16. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell*, 2015; 28(6): 690-714.
17. Chen Y-L, Chang M-C, Cheng W-F. Metronomic chemotherapy and immunotherapy in cancer treatment. *Cancer Lett*, 2017; 400: 282-292.
18. Kumar MNVR, Sood AK. Editorial–Metronomic chemotherapy. *Cancer Lett*. 2017; 100(400): 203.
19. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *Am J Hematol*, 2020; 95(5): 548-567.
20. Nikiforov M, Fink EE, Lipchick B. Multiple myeloma drug resistance: all roads lead to KLF9. *Clin Lymphoma, Myeloma Leuk*, 2015; 15: e225.
21. André N, Tsai K, Carré M, Pasquier E. Metronomic chemotherapy: direct targeting of cancer cells after all? *Trends in Cancer*, 2017; 3(5): 319-325.
22. Simsek C, Esin E, Yalcin S. Metronomic Chemotherapy: A Systematic Review of the Literature and Clinical Experience. *J Oncol*, 2019; 2019: 5483791. doi:10.1155/2019/5483791
23. Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. *Blood*, 2015; 125(20): 3076-3084.
24. Papanikolaou X, Szymonifka J, Rosenthal A, et al. Metronomic therapy is an effective salvage treatment for heavily pre-treated relapsed/refractory multiple myeloma. *Haematologica*, 2013; 98(7): 1147 LP-1153. doi:10.3324/haematol.2013.085183.
25. Maiti R. Metronomic chemotherapy. *J Pharmacol Pharmacother*, 2014; 5(3): 186.
26. Kareva I, Waxman DJ, Klement GL. Metronomic chemotherapy: an attractive alternative to maximum tolerated daose therapy that can activate anti-tumor immunity and minimize therapeutic resistance. *Cancer Lett*, 2015; 358(2): 100-106.
27. Banavali S, Pasquier E, Andre N. Targeted therapy with propranolol and metronomic chemotherapy combination: sustained complete response of a relapsing metastatic angiosarcoma. *Ecancermedicalscience*, 2015; 9.
28. Moreau P, Touzeau C, Vij R, Goldsmith SR, Rosko AE. Newly Diagnosed Myeloma in 2020. *Am Soc*

Clin Oncol Educ B, 2020; (40): 1-15. doi:10.1200/edbk_280221
29. Mpekris F, Baish JW, Stylianopoulos T, Jain RK. Role of vascular normalization in benefit from metronomic chemotherapy. *Proc Natl Acad Sci*, 2017; 114(8): 1994-1999.
30. Guo J, Zhao Y, Fei C, et al. Dicer1 downregulation by multiple myeloma cells promotes the senescence and tumor-supporting capacity and decreases the differentiation potential of mesenchymal stem cells. *Cell Death Dis*, 2018; 9(5): 512. doi:10.1038/s41419-018-0545-6.
31. Revon-Rivière G, Banavali S, Heississen L, et al. Metronomic chemotherapy for children in low-and middle-income countries: survey of current practices and opinions of pediatric oncologists. *J Glob Oncol*, 2019; 5: 1-8.
32. Galieni P. Intermittent Low-Dose Thalidomide Plus Dexamethasone as Maintenance Therapy in Patients with Multiple Myeloma. *Ann Hematol Oncol*, 2019; 6. doi:10.26420/annhematoloncol.2019.1235
33. Srivastava K, Hu J, Korn C, et al. Postsurgical adjuvant tumor therapy by combining anti-angiopoietin-2 and metronomic chemotherapy limits metastatic growth. *Cancer Cell*, 2014; 26(6): 880-895.
34. Bocci G, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: a neglected but crucial aspect. *Nat Rev Clin Oncol*, 2016; 13(11): 659.
35. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*, 2015; 33(26): 2863.
36. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*, 2015; 16(4): 375-384.
37. Heidari A. Chemotherapy a last resort for cancer treatment. *Chemo Open Access*, 2016; 5(4): e130.
38. Mateos M-V, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet*, 2020; 395(10218): 132-141.
39. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*, 2014; 15(12): e538-e548.
40. Printz C. New treatments highlighted for lymphoma and multiple myeloma. *Cancer*, 2015; 121(10): 1530-1531.
41. Munzone E, Colleoni M. Clinical overview of metronomic chemotherapy in breast cancer. *Nat Rev Clin Oncol*, 2015; 12(11): 631.