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Hypoxia: Progressive Multiple Myeloma and Its Therapy Resistance

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ABSTRACT

This study critically reviews the role of hypoxia in the progression of Multiple Myeloma (MM) and its therapy resistance. It explains the existence and role played by Hypoxia Inducible Factors (HIF) including HIF-1α and HIF-β in tumor (MM) progression. These HIF are key transcription factors of hypoxia and they aid the cellular adaptation of both normal and cancer cells to reduction in oxygen concentration. At initial stage of MM, the bone marrow environment sufficiently supports the growth and survival of the MM cells, but as the disease progresses and the plasma cells goes deeper into the bone marrow, they experience a more hypoxic condition. This then activates HIF-1 and HIF-2 which ultimately stimulates angiogenic factors. This is a description of the step by step approaches through which a review of Hypoxia: progressive multiple myeloma and its drug resistance was conducted using Google scholar and PubMed search engines to search articles published from 2000 to May 2020 using the following key words: hypoxia, progressive multiple myeloma, treatment resistance, hypoxia and multiple myeloma. This review suggests that agents capable of inhibiting the action of HIF's, as well as those that would act specifically on the hypoxic zones will be helpful in minimizing/eliminating drug resistance and relapses in MM patients and would invariably improves the patient life expectancy.

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Introduction

Hypoxia is a non-physiological level of oxygen tension, which is a common phenomenon in majority of malignant tumor (1). Humans response to hypoxia is characterized by systemic changes in respiratory, hematopoietic, and cardiovascular physiology which combines to restore sufficient oxygenation (2). Tumor-hypoxia results in vascularization and acquisition of epithelial-to-mesenchymal transition phenotype which leads to cell mobility and metastasis (1). Because of the numerous contributions of hypoxia to radio resistance, chemo resistance, vasculogenesis, angiogenesis, metastasis, invasiveness, resistance to cell death, altered metabolism, and genomic instability, it is a negative predictive and prognostic factor. Tumors have a more severe effect of hypoxia when compared to normal tissues, and hypoxia plays a very significant role in the development of tumor and therapy resistance which owing to this effect, it is been represented as a compelling therapeutic target (3). HIF-1 is a transcription factor which is responsible for the adaptive responses to the reduction in oxygen availability, including glycolysis and angiogenesis. There is a dramatic increase in hypoxic cells due to the oxygen-regulated HIF-1α subunit expression and transcriptional activity (4). The main actors of hypoxic responses are the transcription factors; HIF-1α and HIF-2 (5).

The etiology of MM; a malignant hematological disease is unknown. The production of a monoclonal Para protein, renal insufficiency, anemia, increased bone marrow (BM) angiogenesis, osteolytic bone lesions, amyloidosis, spontaneous fractures, hypercalcemia, and severe bone pain are the key clinical features of MM (6).MM remain

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incurable, records high rate of drug resistance and relapses, with patients currently having an overall median survival of 44 months (7).

A hypoxic tumor environment arises when there is transient limitation in the perfusion of blood or when rapidly proliferating cells outgrows the existing vasculature. Two major strategies have been developed in order to target tumor hypoxia in cancer treatment (6-9).

The introduction of novel agents, including bortezomib in combination with autologous stem cell transplantation, has led to a significant advancement in the treatment of patients, leading to complete response in many patients. Unfortunately, most patients ultimately relapse due to the presence of surviving tumor cells at the minimal residual disease (MRD) state, suggesting the presence of drug resistance within specific niches in the bone marrow. Drug resistance remains a major clinical challenge for cancer treatment. Novel drugs that regulate metabolic pathways in MM, specifically targeting LDHA, can be beneficial to inhibit tumor growth and overcome drug resistance (10-15). Unlike the normal cells which responds homogenously to chemotherapeutic drugs, the malignant cells due to the heterogeneous population of the cells with its different sensitivity levels to chemotherapy, results in some of the cells being easily eliminated by the drugs while others may become totally resistant. Cancer cells may however, become cross-resistant to various drugs which results to a situation known as multiple drug resistance (16).

Despite the current efficient therapeutic regimens for MM patients, the major concern is still drug resistance. For example, in the use of bortezomib as a first class drug in MM, there is usually an intrinsic resistant to it or resistant development in the course of the treatment by most patients. Even though the real mechanism of resistance to bortezomib in MM patients are yet to be understood, mutation in beta 5-subunit of proteasome (conflicting reports),derangement of stress response,survival and antiapoptotic pathways have been indicated to be involved (10, 15)

Following one or more treatment regimen encompassing: corticosteroids, alkylating agents, anthracyclines, proteasome inhibitors, immunomodulatory drugs, histone deacetylase inhibitors and monoclonal antibodies(which when used rationally improves survival outcomes to a greater extent), MM patients relapse successively or become refractory, mostly as a result of drug resistance (16) Histories of MM patients are characterized by multiple relapses which usually occurs following different lines of treatment until becoming refractory (16, 17).

Methods

This is a description of the step by step approaches through which a review of Hypoxia: progressive multiple myeloma and its drug resistance was conducted using Google scholar and PubMed search engines to search articles published from 2000 to May 2020. Except one article of 1975 which was used to compare recent findings. Articles were searched using the following key words: “hypoxia”, “progressive multiple myeloma”, “treatment resistance”, “hypoxia and multiple myeloma”.

Results

Seventy articles were searched using the following key words: hypoxia, progressive multiple myeloma, treatment resistance, hypoxia and multiple myeloma. Out of the seventy articles searched, 49 relevant articles were selected. The selection criteria used in the inclusion of a study were basically on its relevance to the topic, and the exclusion criteria encompasses old data and studies not relevant to the topic. In Table 1 selected studies are listed.

Table 1. Selected studies from google scholar and pubmed.

SELECTED STUDIES	TOPICS OF SELECTED STUDIES
Muz et al.,	The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy
Smith et al.,	The human side of hypoxia-inducible factor
William et al.,	Targeting hypoxia in cancer therapy
Semenza	Hypoxia, clonal selection, and the role of HIF-1 in tumor progression
Semenza	Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics
Martin et al.,	The emerging role of hypoxia, HIF-1, and HIF-2 in multiple myeloma,
Kumar et al.,	Improved survival in MM and the impact of novel therapies

Table 1. Continued.

Jinsong et al.,	Understanding the hypoxic niche of MM: therapeutic implications and contributions of mouse models
Le QT et al.,	Hypoxic gene expression and metastasis
Abdi et al.,	Drug resistance in MM: latest findings and new concepts on molecular mechanisms.
Ullah et al.,	A major impediment to effective chemotherapy
Gottesman	Mechanism of cancer drug resistance
Sonneveld	Multidrug resistance in hematological malignancies.
Garraway and James	Circumventing cancer drug resistance in the era of personalized medicine
Wang	The resistance mechanism of proteasome inhibitor bortezomid
Hugo et al.,	MM: Available therapies and causes of drug resistance
Dimopoulos et al.,	Current treatment landscape for relapsed and/or refractory MM.
Rajkumar et al.,	Diagnosis and Staging of MM and Related Disorders
Durie and Salmon	A clinical staging system for MM. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival
Griepp et al.,	Revised international staging system for multiple myeloma: a report from International Myeloma Working Group
Paleolog	Hypoxia: not merely a regulator of angiogenesis?
Bhaskar et al.,	HIF-1α and MM
Pouysseguar	Hypoxia signalling in cancer and approaches to enforcetumour regression.
Bos et al.,	Levels of HIF-1α during breast carcinogenesis
Hoffmann et al.,	High expression of HIF-1α is a predictor of clinical outcome in patients with pancreatic ductal adenocarcinomas and correlated to PDGFA, VEGF, and Bfgf
Birner et al.,	Expression of HIF-1α in epithelial ovarian tumors: its impact on prognosis and on response to chemotherapy
Theodoropoulos et al.,	HIF-1α expression correlates with angiogenesis and unfavorable prognosis in bladder cancer.
Hu et al.,	Targeting the MM hypoxic niche with TH-302, a hypoxia-activated prodrug
Asosingh et al.,	Role of the hypoxic bone marrow microenvironment in 5T2MM murine myeloma tumor progression.
Martin et al.,	HIF-2 is a novel regulator of aberrant CXCL12 expression in MM plasma cells.
Holmquist-Mengelbier et al.,	Recruitment of HIF-1alpha and HIF-2alpha to common target genes is differentially regulated in neuroblastoma: HIF-2alpha promotes an aggressive phenotype
Carmeliet and Jain	Angiogenesis in cancer and other diseases

Table 1. Continued.

Giatromanolaki et al.,	Hypoxia and activated VEGF/ receptor pathway in MM
Palumbo et al.,	Revised international staging system for MM. International myeloma working group
Ria et al.,	Bone marrow angiogenesis and progression in MM
Karakashev and Reginato	Progress toward overcoming hypoxia_induced resistance to solid tumor therapy
Muz et al.,	Hypoxia promotes stem cell-like phenotype in MM cells.
Prahlad et al.,	TrxR1 inhibition overcomes both hypoxia-induced and acquired bortezomib resistance in MM through NF-kb
Shin et al.,	Bortezomib inhibits tumor adaptation to hypoxia by stimulating the FIH-mediated repression of HIF-1
Zhang et al.,	Targeting angiogenesis via a c-Myc/HIF-1α-dependent pathway in MM.
Lu et al.,	The anti-cancer drug lenalidomide inhibits angiogenesis and metastasis via multiple inhibitory effects on endothelial cell function in normoxic and hypoxic conditions
Mitsiades et al.,	Antimyeloma activity of heat shock protein-90 inhibition
Hu et al.,	Inhibition of HIF-1 function enhances the sensitivity of MM cells to melphalan
Yeo et al.,	YC-1: a potential anticancer drug targeting HIF-1
Welsh et al.,	Antitumor activity and pharmacodynamics properties of PX-478, an inhibitor of HIF-1α
Greenberger et al.,	A RNA antagonist of HIF-1α EZN-2968, inhibits tumor cell growth
Olenyuk et al.,	Inhibition of vascular endothelial growth factor with a sequence-specific hypoxia response element antagonist.
Pack et al.,	Targeting the PAS-A domain of HIF-1alpha for development of small molecule inhibitors of HIF-1
Kong et al.,	Echinomycin, a small-molecule inhibitor of HIF-1 DNA-binding activity.

Multiple myeloma progression

People do not often experience MM symptoms until they reach stage 3. At this stage, the cancer affects multiple areas of the body, causing complex symptoms (18).

All cancers are divided into different stages, so as to indicate the degree of its progression in a patient. Staging of MM has been traditionally done using the Durie-Salmon Staging (DSS) (19) or the International Staging System (ISS) (20). The DSS primarily classified patients based on tumor burden, while the ISS also includes a host factor determinant, namely, serum albumin. The main disadvantage of these older staging systems is that outcome in MM unlike many other malignancies is dependent more on disease biology.

To rectify this, a Revised International Staging System (RISS) has been adopted by the IMWG that combines the ISS with determinants of disease biology. The RISS incorporates determinants of disease biology (the presence of high risk cytogenetic abnormalities or elevated lactate dehydrogenase level) into the former ISS to create 3 disease stages;

-Stage II; Neither stage I or III

-Stage III; ISS stage III (serum beta-2-microglobulin >5.5) or High-risk cytogenetics (21)

Neovascularization which is a constant hallmark of MM progression is a clinically important aspect of MM plasma cells interaction with the bone marrow microenvironment (22).

Hypoxia in progressive multiple myeloma (MM)

Studies have demonstrated that hypoxia does more than regulate angiogenesis, it also provides an important

environment for angiogenesis to occur (23). Rapid tumour growth usually elicits a state of hypoxia in its local ambience (24). Hypoxic responses induce angiogenic factor and growth factors which invariable leads to the formation, growth and development of blood vessels. Hypoxia in tumours is mediated by an upregulation of the transcription factor HIF-1 complex. Pagasseur et al revealed that while HIF-1a is a cytoplasmic protein that is dependent on O2 levels, HIF-1β on the other hand is a nuclear protein that is constitutively expressed irrespective of O2 level (25).

Increased expression of HIF-1α and HIF-2β is a key indicator of number of malignancies like cancer of the breast, kidneys, pancreas, bladder, bone, ovary, lung, colon (26-28).The overexpression of HIF in tumours arises not only from the aberrant nature of HIF-1α activation induced by oncogenes, but also the hypoxic nature of the tumour (24). HIF-1α typifies a highly aggressive disease phenotype as it is overexpressed in over 70% of human cancers (26, 28, 29) and is related to progression free survival in several human cancers (27-29).

One of the key characteristics of MM is the accumulation of malignant plasma cells in the bone marrow environment. The bone marrow microenvironment is naturally hypoxic and this is pivotal for the normal hematopoietic process of the bone marrow. The myelomatous BM environment is more hypoxic than the natural bone marrow environment (24). Recent studies using 5T33MM murine model of MM buttresses the point that the myelomatous BM microenvironment is more hypoxic than the normal BM microenvironment (30). In addition, studies by Asosingh et al using the 5T2MM mouse models of MM suggests that the hypoxic BM microenvironment plays a role in the establishment of MM, following the migration of the MM Pc from secondary lymphoid organs to the bone marrow (31).

In the initial stages of the MM, the BM environment is sufficient to support the growth and survival of the MM cells (6, 31). However, as the disease progresses and the plasma cells of the MM gets deeply entrenched within the endothelial niche of the bone marrow, their level of exposure to hypoxia increases even further. This overexposure to hypoxia activates HIF-1/ HIF-2 and this in turn stimulates angiogenic factors, which subsequently increases oxygen delivery to the tumour cells, thus promoting tumour growth (24).

Critical evaluation of temporal modulation of HIF-1α and HIF-2α expression in MM cell lines in response to hypoxia reveals that there is a rapid upregulation of the HIF-1α protein, whereas for the induction of the HIF-2α protein there is a relatively delayed response to hypoxia (32) the above process connotes an immediate and clear response of HIF-1 to hypoxia. However, HIF-2 coordinates responses to more prolonged and chronic hypoxia (33).

One of the most documented consequence of an aberrant HIF expression has been shown to be angiogenesis. Angiogenesis is essential for tumour growth and also constitutes an important target in the control of the progression of tumours (34) Studies have shown a positive correlation between HIF-1α and HIF-2α expression, the degree of BM angiogenesis and the expression of VEGF(35). HIF-1α is an important regulator of vascular endothelial growth factor (VEGF) in MM cells as it regulates BM angiogenesis through the VEGF and VEGF is often associated with poor prognosis in MM patients (24).

Hypoxia in multiple myeloma treatment resistance

Hypoxia leads to the alteration of cancer cell metabolism and contribute to therapy resistance by the induction of cell quiescence (dormancy or no growth and no division) (1). In order to adjust to the hypoxic microenvironment, the transcription factor HIF-1α modulates several genes in tumor cells and this allows tumor proliferation, cell survival, invasion, angiogenesis and then drug resistance (36).

Relapse and micro residual disease in MM may be attributed to the development of a stem cell-like subpopulation which demonstrates therapy resistance and causes recurrence. The effect of hypoxia on MM cell proliferation in the presence of proteasome inhibitors was investigated. The evidence of hypoxia to decrease reactive oxygen species production led to the suggestion that it could be a potential mechanism of resistance to proteasome inhibitors in hypoxia in MM cells (37).

The effect of hypoxia on nuclear factor keppa beta P65 expression in myeloma cells have been examined. Higher antioxidant level may correlate with poor prognosis and clinical outcome in MM and other cancers. And therefore, thiorezomib-drugs like auranofin; used either as a single agent or a combination therapy to circumvent bortezomib resistance in MM and improves survival outcome of MM patients is being proposed (38).

Two major strategies have been developed in order to target tumor hypoxia in cancer treatment and they include the use of drugs that will inhibit the molecular targets in the hypoxia signaling pathway like HIF-1α inhibitor, and the use of bio reductive prodrugs that are selectively activated by hypoxia (8). HIF-1α activity have been shown to be inhibited by a number of anti-MM drugs which encompasses: bortezomib ,adaphostin, lenalidomide, and 17-AAG (39-43) According to Jinsong et al, the targeting of HIF-1a in hypoxic tumor cells with more specific small-molecule inhibitors – which includes YC-1,PX-478,EZN-2968,Polyamide 2,NSC 50352, and Echinomycin–are being developed and tested in different solid tumors (44-49)

Conclusion

Despite several front line remedies available for MM patients, most patients unfortunately experience relapse

and develop progressive disease leaving only a restricted choice of treatment for them. Since the main actors of hypoxic responses are the transcription factors; HIF-1α and HIF-2. In order to adjust to this hypoxic microenvironment, the transcription factor HIF-1α modulates several genes in tumor cells and this allows tumor proliferation, cell survival, invasion, angiogenesis and then drug resistance. Several cascades of responses elicited by the hypoxic nature of the BM microenvironment accounts for progressive MM and its therapy resistance. Sequel to this, this review suggests that agents capable of inhibiting the action of HIF's, as well as those that would act specifically on the hypoxic zones will be helpful in minimizing/eliminating drug resistance and relapses in MM patients and would invariably improves the patient life expectancy.

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References

1. World Health Organization. Introduction to Drug Utilization Research. [Internet]. Oslo, Norway: WHO; 2003 [cited 2020 Dec 22]. Available from: https://apps.who.int/iris/handle/10665/42627

2. Fallik B. The Academy of Managed Care Pharmacy's concepts in managed care pharmacy: prior authorization and the formulary exception process. J Manag Care Pharm 2005;11(4):358-61.

3. Bergmans DC, Bonten MJ, Gaillard CA, et al. Indications for antibiotic use in ICU patients: a one-year prospective surveillance. J Antimicrob Chemother 1997;39(4):527-35.

4. Shoaei SD, Bagherzadeh A, Haghighi M, Shabani M. Vancomycin and five broad-spectrum antibiotic utilization evaluation in an educational medical center in one year. Journal of Pharmaceutical Care 2014;2(4):154-61

5. Soltani R, Khorvash F, Pazandeh F. Antimicrobial resistance pattern of nosocomial infections at a referral teaching hospital. Journal of Pharmaceutical Care 2020;8(1):26-34.

6. Singh N, Victor LY. Singh N, Yu VL. Rational empiric antibiotic prescription in the ICU. Chest 2000;117(5):1496-9.

7. Hatcher JC, Dhillon R, Azadian B. Antibiotic resistance mechanisms in the intensive care unit. J Intensive Care Soc 2012;13(4):297-303.

8. Bisht R, Katiyar A, Singh R, Mittal P. Antibiotic resistance – A global issue of concern. Asian J Pharm Clin Res 2009; 2(2): 34-9.

9. Hashemi S, Nasrollah A, Rajabi M. Irrational antibiotic prescribing: a local issue or global concern? EXCLI J 2013;12:384-95.

10. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63(5):e61-e111.

11. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70(3):195–283.

12. American Pharmacists Association (APhA). Drug Information Handbook: A Clinically Relevant Resource for All Healthcare Professionals. 26th ed. Ohio: Lexi-Comp; 2017-2018.

13. Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015.

14. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill Medical; 2017.

15. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, Pavia AT, Black D, Freedman DO, Kim K, Schwartz BS, editors. The Sanford guide to antimicrobial therapy. Antimicrobial Therapy, Inc.; 2020.

16. Zarezadeh M, Shaterzadeh F, Abedini S, Raadabadi M. Evaluating pattern of prescribing antibiotics in surgical wards of shahid rahnemon hospital compared to standard methods in 2015. Journal of Shahid Sadoughi University of Medical Sciences 2015;23(7):679-690.

17. Mahini S, Hayatshahi A, Torkamandi T, Gholami K, Javadi MR. Carbapenem utilization in critically Ill patients. Journal of Pharmaceutical Care 2013;1(4):141-144.

18. Rafati M.R, Sahraee S, Zamani Z, Irvash M. Antibiotics Usage in Intensive Care Unit in Sari Bouali Sina Hospital. Journal of Mazandaran University of Medical Sciences 2015; 24(122):12-22.

19. Kazmierczak KM, Biedenbach DJ, Hackel M, et al. Global dissemination of blaKPC into bacterial species beyond Klebsiella pneumoniae and in vitro susceptibility to ceftazidime-avibactam and aztreonam-avibactam. Antimicrob Agents Chemother 2016;60(8):4490-500.

20. Lee C-R, Lee JH, Park KS, Kim YB, Jeong BC, Lee SH. Global dissemination of carbapenemase-producing Klebsiella pneumoniae: epidemiology, genetic context, treatment options, and detection methods. Front Microbiol 2016;7:895.

21. Spyropoulou A, Papadimitriou-Olivgeris M, Bartzavali C, et al. A ten-year surveillance study of carbapenemase-producing Klebsiella pneumoniae in a tertiary care Greek university hospital: predominance of KPC-over VIM-or NDM-producing isolates. J Med Microbiol 2016;65(3):240-6.

22. Wiseman LR, Wagstaff AJ, Brogden RN, Bryson HM. Meropenem. A review of its antibacterial activity, pharmacokinetic properties and clinical effcacy. Drugs 1995;50(1):73-101.

23. Naderi P, Shirani K, Soltani R, Khorvash F, Naji Esfahani SS. Meropenem utilization evaluation in a referral teaching hospital in Iran. J Res Pharm Pract 2018;7(2):83-7.

24. Yong D, Lee K, Yum JH, et al. Imipenem-EDTA disk method for differentiation of metallo-beta-lactamase-producing clinical isolates of Pseudomonas spp. and Acinetobacter spp. J Clin Microbiol 2002;40(10):3798-801.

25. Lee K, Ha GY, Shin BM, et al. Metallo-beta-lactamase-producing gram-negative bacilli in Korean Nationwide Surveillance of Antimicrobial Resistance group hospitals in 2003: Continued prevalence of VIM-producing Pseudomonas spp. And increase of IMP-producing Acinetobacter spp. Diagn Microbiol Infect Dis 2004;50(1):51-8.

26. Khan MU, Yousuf RI, Shoaib MH. Drug utilization evaluation of meropenem and correlation of side effects with renal status of patients in a teaching based hospital. Pak J Pharm Sci 2014;27(5 Spec no):1503-8.

27. Dew R.S, Radji M, Andalusia R. Evaluation of Antibiotic Use Among Sepsis Patients in an Intensive Care Unit A cross-sectional study at a referral hospital in Indonesia. Sultan Qaboos Univ Med J 2018;18(3):e367-e373.