Minireview

Role of hyperoxic treatment in cancer

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Impact statement

Tumor hypoxia promotes cancer cell aggressiveness, and is strongly associated with poor prognosis across multiple tumor types. The hypoxic microenvironments inside tumors also limit the effectiveness of radiotherapy, chemotherapy, and immunotherapy. Several approaches to eliminate hypoxic state in tumors have been proposed to delay cancer progression and improve therapeutic efficacies. This review will summarize current knowledge on hyperoxia, used alone or in combination with other therapeutic modalities, in cancer treatment. Molecular mechanisms and undesired side effects of hyperoxia will also be discussed.

Abstract

The occurrence of hypoxia is common in many solid tumors, and it enhances aggressive features of cancer such as cell survival, angiogenesis, and metastasis while minimizing the efficacies of chemotherapy and radiotherapy. Hypoxia also plays a pivotal role in regulating immune cell function which is important for immunotherapy. Hypoxia-inducible factor has been suggested as a master regulator of tumor cell adaptation to the hypoxic microenvironment. Currently, several approaches have been proposed to eliminate the hypoxic state in tumors for delaying cancer progression and improving therapeutic efficacy. In this review, we summarize current findings on the relevance of hyperoxia-based therapeutics for cancer treatment. Accumulating evidence indicates that hyperoxic therapy inhibits tumor growth and increases treatment efficacy. Primary antitumor effect of hyperoxic therapy may be due to the reversal of tumor hypoxia and the generation of reactive oxygen species. Restoring immune function is also suggested as a potential mechanism. Hyperoxic therapy can also cause cellular injury and organ dysfunction. In conclusion, overcoming tumor hypoxia is a major problem that needs to be solved. Further studies to standardize and personalize hyperoxia therapy according to the type of cancer, stage, and comorbidities are needed.

Keywords: Neoplasms, hyperoxia, oxygen, reactive oxygen species, oxidative stress, antitumor effect

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Introduction

Oxygen is an indispensable element for cells in our body to fulfill energy requirement from aerobic metabolism. Therefore, reduced oxygen levels, hypoxia, may produce cell death and resulting organ dysfunction as occurs in heart attacks or strokes. Hypoxia commonly arises in the core of most solid tumors as a result of an inadequate supply of oxygen from abnormal vasculature, and an increased oxygen demand from changes in tumor metabolism.[1] Severity of tumor hypoxia varies depending on tissue of origin and tumor size, and median oxygen levels in untreated tumors are frequently less than 2% in comparison to the normal human tissues (5%).[2,3] The hypoxic regions within the tumor are heterogeneously distributed and may even located near to vessels.[4]

Traditionally, hypoxia was thought of as a factor limiting the cancer growth by reducing the ability of cells to divide.[5] However, increasing evidence indicates that tumor hypoxia plays an important role in cancer progression. When tumor cells adapt to the imbalance between oxygen supply and demand, malignant features of solid tumors such as resistance to cell death, angiogenesis, and metastasis were invariably enhanced.[6,7] Emerging features of cancer development such as genome instability, the enrichment of cancer stem cells, and aberrant exosomal secretion were also suggested as hallmarks of tumor hypoxia.[8–10] Overall, hypoxic microenvironment in tumor promotes acquisition of the more aggressive cancer phenotypes and thus is associated with poor prognosis.[11,12] In addition, tumor hypoxia has been considered as one of the biggest barriers to treating cancer because it renders tumors more

resistant to surgery, radiotherapy, chemotherapy, and immunotherapy.[13–16] In this regard, it is widely accepted that hypoxia is a potential cancer-specific target,[11,17] and several approaches targeting tumor hypoxia for cancer therapy such as erythropoietin, nicotinamide, hypoxia-activated prodrugs, and nanocarriers have been proposed.[14,18]

Numerous studies also suggest increasing oxygen content using hyperoxia as a promising therapeutic modality to reverse tumor hypoxia as well as resistance to cancer therapeutics.[5,19–21] Recently, we also identified anti-cancer effect of hyperoxia and its mechanism of action in mouse lung cancer.[22,23] However, despite of growing interest and clinical trials, the application of hyperoxia to cancer treatment is still in its nascent stage. Here, we will focus on the recent insights into the understanding of hyperoxia-mediated cancer treatment.

Hyperoxic therapy in cancer

Oxygen therapy is a type of treatment to enhance the amount of dissolved oxygen in the plasma by breathing supplemental oxygen, thereby increasing O_2 delivery to body tissue. For hyperoxygenation, 100% oxygen is administered to a patient either at ambient atmospheric pressure (normobaric oxygen, NBO) or under hyperbaric conditions usually in a pressurized chamber (hyperbaric oxygen, HBO). Oxygen therapy has long been regarded as integral to the management of various medical conditions for centuries. For cancer treatment, there is still no evidence that it is effective in treating cancer.[24] However, despite ongoing controversy, interest in applying hyperoxic therapy as adjuvant for cancer treatment is rapidly growing. For example, in Pubmed search concerning oxygen therapy and cancer, since the first article in 1951,[25] more than 20,000 were found. A brief summary of hyperoxic therapies on cancer is listed in Table 1.

In addition to oxygen breathing, although relatively uncommon, other forms of oxygen therapy such as oxygen-containing substances (i.e. ozone or hydrogen peroxide), and prodrugs that are activated only in the hypoxic tumor environment also have been tried for cancer treatment.[32–34]

Hyperbaric oxygen therapy

HBO treatment is breathing 100% oxygen at higher atmospheric pressure usually between 1.5 and 3 atm which enable the lungs to receive more oxygen up to three times than under normal air pressure, resulting in immediate saturation of plasma with oxygen. In normal subject, compared to normobaric air, HBO at 3 atm increases both arterial (from 100 to 2000 mmHg) and tissue (from 55 to 500 mmHg) oxygen tensions (PO_2).[35] Similarly, the PO_2 level was significantly increased in tumor tissue by HBO exposure, demonstrating three to four times greater hyperoxygenation effect in tumor tissue than NBO.[36,37] Therefore, HBO rather than NBO has been preferentially used to eliminate poorly oxygenated regions of tumor which play a major role in tumor development and resistance to other therapeutic modalities. In addition, HBO therapy is considered safe and well tolerated, and side effects are rare.[38] Although several studies showed the favorable outcomes of HBO by itself in cancer treatment,[5,28,39] HBO alone gives a limited curative effects, and it even enhances tumor growth.[19,40] Accordingly, HBO is preferentially used as an adjuvant treatment for enhancing tumor sensitivity and decreasing complications of other therapies.[34]

Normobaric oxygen therapy

NBO therapy is a routine adjuvant oxygenation intervention supplied by nasal cannula or facemask under ambient pressure. For cancer treatment, NBO is an attractive alternative to HBO due to its ease of administration and lower complication in actual clinical practice.[41] However, when compared to HBO, effect of NBO on arterial and tissue oxygenation is much weaker. Arterial PO_2 in aorta has increased only 4-fold after exposure to NBO (345 vs. 84.1 mmHg).[42] In animal study, most of tumors were nearly anoxic (PO_2 <1 mmHg), but NBO immediately increased PO_2 (mean >25 mmHg) and remained elevated during gas exposure.[43] Accordingly, NBO treatment significantly retarded tumor growth.[39,44] We also previously showed the NBO inhibits lung cancer in *in vivo* and *in vitro* through reactive oxygen species (ROS) generation and apoptosis.[23]

Molecular mechanisms: Hypoxia-inducible factor 1α

Hypoxia

When oxygen levels in tumor microenvironment are dropping, transcriptional induction of a series of genes necessary for maintaining cell survival/proliferation and promoting more aggressive features occurs in tumor cells. These oxygen-dependent responses are tightly regulated by HIF-1α, the master transcriptional regulator of the hypoxic response as well as a representative endogenous biomarker for hypoxia.[45]HIF-1α is induced by hypoxia through post-translational modification, and it binds to specific recognition sequences in the genome to increase the expression of HIF-1α target genes.[46] Since the seminal discovery of HIF in the early 1990s by Gregg Semenza, a Nobel Laureate in Physiology or Medicine for 2019,[47] thousands of genes are identified as direct targets of HIF-1α,[48] and therefore a myriad of changes associated with tumor aggravation occur in hypoxic tumor cells including angiogenesis and oxygen supply, stemness/self-renewal, proliferation, epithelial to mesenchymal transition, metastasis and invasion, redox homoestasis, anti-apoptosis, and metabolic reprogramming.[49,50] Metabolic reprogramming from oxidative phosphorylation to accelerated glycolysis in cancer cells is also known to be mediated via HIF-1α.[51] In addition, HIF-1α contributes to the development of tumor resistance to therapeutic approaches and serves as a promising biomarker.[52,53] For example, HIF-1α limits T cell recognition of tumor cells by downregulating MHC class I

Table 1. Summary of studies on cancer with hyperoxic therapies.

References	Year	Type of tumor	Type of hyperpoxic treatment	Combination treatment	Summary of the study
Moen *et al.*[26]	2009	DMBA-induced mammary tumor mouse model	2 bar, $pO_2 = 2$ bar, 4 times (day 1, 4, 7 and 10) exposures of 90 min	5-FU	HBO increases the uptake of [^{3}H]-5FU
Kawasoe *et al.*[27]	2009	Osteosarcoma LM8 cells mouse model	2.5 bar, $pO_2 = 2.5$ bar, 60 min, 5 times a week until 5 weeks	Carboplatin	HBO or HBO with carboplatin inhibits tumor growth and lung metastasis, synergistically
Selvendiran *et al.*[28]	2010	A2780 ovarian xenograft tumor mouse model	100% O_2 2 atm for 90 min, 21 days	Cisplatin	Reduction of tumor volume. No significance between HBO and cisplatin-treated group
Sun *et al.*[29]	2012	Human glioblastoma multiforme cells (D54, U87)	40%, 80% O_2, 72 h	Temozolomide	NBO enhanced TMZ toxicity in GBM cells
Lee *et al.*[30]	2014	Human glioblastoma multiforme cells (D54, U87, U251)	40% O_2, 24, 48 and 72 h	Temozolomide	NBO enhanced the sensitivity to temozolomide in chemosensitive and -resistant GBM cells
Hatfield *et al.*[31]	2016	MCA205 fibrosarcoma mouse model	60% O_2, 72 h and 11 days	–	NBO reverses the hypoxia–A2-adenosinergic immunosuppression during acute inflammation
Yttersian Sletta *et al.*[21]	2017	Breast cancer mouse model	2.5 bar, $pO_2 = 2.5$ bar, 90 min, every third day until day 16	5-FU	Suppressed tumor growth and metastatic lesions, HBO does not enhance the 5-FU efficacy
Kim *et al.*[23]	2018	Lewis lung carcinoma cell injected mouse model	24 h NBO (95% O_2)/normoxia cycle for two weeks	–	NBO inhibits the progression of lung cancer by inducing apoptosis
Lee *et al.*[22]	2018	benzo[a]pyrene -induced lung tumorigenesis mouse model	95% O_2 for 3 h/day, days 21–28	Carboplatin	Intermittent NBO with carboplatin displays a synergistic tumoricidal effect
Qian *et al.*[20]	2019	triple-negative breast cancer mouse model	60% O_2, day 7-28	–	NBO reverses immunosuppression and control the extend of lung metastases

molecule expression.[54] It also induces multidrug resistance, the major cause of chemotherapy failure, by inducing multidrug resistance-associated protein 1 in cancer cells.[55] Accordingly, in cancer patients, protein levels of HIF-1α in solid tumors are considered as a critical prognostic factor.[56] Based on these findings, HIF-1α has become targets for developing novel cancer therapeutics. However, no agents directly inhibiting HIF-1α have been approved for treating cancer patients.[57]

Hyperoxia

Many reports suggest various beneficial effects of hyperoxia on hypoxic tumor. Hyperoxic breathing of 60% O_2 recovers oxygen homeostasis in tumor microenvironment hypoxia to normoxia, inhibits survival/proliferation, stemness, and immune escape of cancer cells, resensitizes chemoresistance, leading to tumor regression.[29,58,59] We also reported anti-cancer effects of hyperoxia, alone or in combination with a chemotherapeutic drug carboplatin, on mouse lung cancer; normobaric hyperoxia significantly induces oxidative stress and apoptosis in tumor tissue and reduces tumor mass and migration/invasion.[22,23] Differential response of cancer and normal cells to hyperoxia has also provided a treatment rationale of hyperoxia in cancer treatment. Basal antioxidant defense levels are aberrant in tumor cells, thus an increased oxidative stress has been observed. Since the superoxide dismutase activity in most tumors are lower than normal tissue, tumor cells show higher susceptibility to increased ROS activity induced by hyperoxia.[60] Synthesis of glutathione (GSH), an antioxidant preventing ROS-induced damage, increases proportional to ambient oxygen tension, but not in cancer cells.[61] In consistent with these findings, we demonstrated that NBO showed anti-tumor activity in lung tumor cells but not in normal lung cells.[23] In addition, hyperoxia is angiogenic in normal tissues, but anti-angiogenic in tumor tissues.[62]

Anti-cancer mechanisms of hyperoxia can also be inferred indirectly from clinical and experimental findings. Roles of HIF-1α in hypoxia-mediated cancer development are widely acknowledged, and hyperoxic treatment has long been used to cure clinical disorders such as hypoxia or ischemic diseases by increasing oxygen delivery to oxygen-deficient tissues. We can also take a hint from well-known mechanisms for the induction and regulation of HIF-1α: HIF-1α protein is subject to degradation through an oxygen-dependent ubiquitination,[63] and hypoxia-induced HIF-1α protein is rapidly decayed within 5 min upon exposure to normoxia (20% O_2).[64] In addition, transcriptional activity of HIF-1α is enhanced by hypoxia-induced ROS,[65] and inhibited by oxygen in nonhypoxic cells.[66] Taken these findings together, it seems reasonable that therapeutic effects of hyperoxia on hypoxic tumor are mediated through not direct regulation of HIF-1α but primarily the reversal of hypoxia and the attenuation of the HIF-mediated effects.

However, despite of accumulating evidence supporting this idea, many reports also indicate HIF-1α–independent effects of hyperoxia on tumor. For example, both normoxia and hyperoxia induces higher levels of HIF-1α than hypoxia in tumors, but tumor grows faster in hypoxia group, suggesting that signaling pathways other than HIF-1α driven response may play important roles for *in vivo* cancer cell proliferation.[67] Recent report also showed that HIF-1α levels in tumor cells was significantly downregulated in hyperoxia (60% O_2) than normoxia (20% O_2), indicating that alternative mechanisms other than simple reversal of tumor hypoxia to normoxia underlie anti-tumor effects of hyperoxia.[59] Coincidentally, Rocco *et al.*[68] suggest that relative changes of oxygen availability rather than steady state hypoxic or hyperoxic conditions play an important role in HIF transcriptional effects. In addition, hyperoxia activates HIF-1α overexpression through the activation of Src oncogene, and also inhibits the stability of HIF-1α by reducing ROS formation.[65,69,70] Despite numerous attempts, mechanisms underlying hyperoxia-mediated anti-cancer activity remain to be elucidated.

Side effects

Hyperoxic therapy is usually well tolerated with an acceptable rate of complications; however, as with all medical treatments, it also includes medical risks. Dependent on the type of hyperoxic therapy, patients may experience two prominent side effects due to exposure to high levels of oxygen (oxygen toxicity) or high atmospheric pressure (barotrauma). As shown above, PO_2 used in HBO therapy is much higher than that of NBO, thus oxygen toxicity is more common in patients exposed to HBO. In addition, only HBO therapy is carried out in a hyperbaric chamber, thus barotrauma occurs only in patients taking HBO therapy.

Oxygen toxicity

Exposure to high concentration of oxygen is well known cause of cell damage. For example, oxygen, at concentrations of 95% or more, is severely cytotoxic to the pulmonary cells of many animal species, including humans.[71] Humans appear more resistant to oxygen-induced damage and the risk of hyperoxic acute lung injury is minimal when the FiO2 is ≤ 0.6[72] but continuous exposure to elevated levels of oxygen may cause oxygen toxicity. Major organs subject to oxygen toxicity are lungs (hyperoxic acute lung injury), central nervous system (loss of consciousness and oxygen toxicity seizure), and eye (hyperoxic myopia and cataract).[73–75] Oxygen toxicity is believed to be mediated primarily by a production of ROS at levels exceeding the capacity of antioxidant defence mechanisms.[76] Following HBO treatment, ROS increased to about 2.14–2.44 fold in mitochondria and 1.32–1.42 fold in whole cell.[77] Reduction of antioxidant enzymes such as superoxide dismutase and glutathione by HBO, but not by NBO, also contributes to increased oxygen toxicity.[78] Excessive ROS can damage all essential macromolecules, including nucleic acids, lipids and proteins, leading to an overall progressive decline in physiological function.[79] For example, protein oxidation

and nitrosylation can impair a wide variety of enzymatic processes and growth factors that can result in marked cellular dysfunction.[80] Lipid peroxidation activates apoptosis through activation of sphingomyelinase and release of ceramide.[81] Nucleic acid oxidation has been linked with aging and DNA strand breaks, leading to necrosis and/or apoptosis.[82] Therefore, HBO-driven ROS can display many harmful activities including the induction of DNA damage, cell death, cellular senescence, and deleterious inflammatory response which in turn exacerbates oxidative toxicity and tissue damage.[83,84] Several mechanisms involved in hyperoxia-induced oxygen toxicity have been proposed. For example, ROS stimulates signaling pathways mediated via protein kinases (Akt, MAPK and PKC), resulting in activation of transcription factors (Nrf2, NF-κB, and AP-1) responsible for cell death and inflammation.[85] In addition, ROS-independent mechanisms such as the induction of apoptosis by direct activation of Bax, Bak, or FAS,[86] chemokine receptor CXCR2-mediated tissue inflammation,[87] and toll-like receptor-linked cell damages[88] also have been suggested.

Barotrauma and other complications

In HBO therapy, unlike to NBO, patients are exposed to the high atmospheric pressure in hyperbaric chamber. Barotrauma, pressure-induced injury, is caused by inability to equalize pressure between the environment and the air-filled space in the body such as lungs, ear, sinuses, eyes, and teeth are concurrently at risk. The most common type of barotrauma (>17%) is middle ear barotrauma which can lead to permanent hearing loss and vertigo.[89]

Some patients can develop a feeling of claustrophobia, the fear of being enclosed in small spaces with no escape, due to the confined nature of hyperbaric chamber. HBO therapy also causes mild increase in blood pressure in both hypertensive and non-hypertensive patients, and hypoglycemia can occur in diabetic patients.[90] In addition, NBO increases pulmonary metastasis of tumor[91] and inhibits glucose-induced insulin release.[92]

Because hyperoxia, unlike hypoxia, is a man-made condition, specific adaptive response to hyperoxia has not been evolved in humans. To enhance safety and to prevent side-effects of HBO therapy in cancer treatment as well as other clinical trials, further investigation to maximize therapeutic efficacy and minimize complications by standardizing therapy protocol in particular with regard to pressure and duration is required.

Role of hyperoxia treatment in chemotherapy

Hypoxia reduces the sensitivity of cancer to chemotherapy.[6] In addition, hypoxic cells do not receive sufficient chemotherapeutic agents due to distance from the capillary and because of abnormal vascularization of tumors. Hypoxia remotes resistance through the HIF-1-mediated upregulation of different genes and signaling pathways.[93] Hypoxia-induced drug resistance is also explained by inhibition of apoptotic pathways[23,94] and increased intracellular drug efflux.[95] Currently, respiratory hyperoxia is mainly used for the treatment of hypoxic tissue damage. Also, hyperoxia has also been shown to improve the treatment efficacy of chemotherapy in animal models.[20,22,26] From our previous study, NBO therapy was found to be tumoricidal and NBO with carboplatin exhibited a synergistic antitumor effect on B[a]P-induced lung cancers in mice.[22,23] Oxidative stress and its effects on DNA are increased following exposure to hyperoxia and even more with chemotherapy, and this may lead to apoptosis of lung tumors. Lee *et al.*[30] showed that NBO treatment resensitizes chemoresistant glioblastoma cells to temozolomide through unfolded protein response.

Other studies were mostly performed under HBO treatment. Moen *et al.*[26] showed that HBO treatment increases the uptake of 5-fluorouracil in mammary tumors for the duration of, and immediately after, HBO treatment. Kawasoe *et al.*[27] showed significant suppression of osteosarcoma with HBO plus carboplatin compared with monotherapy, both in *in vitro* and *in vivo.* Other studies also showed increased efficacy against variety of malignancies with combination of HBO and chemotherapy.[28,96,97] However, precise mechanisms are not known until now and more standard combination treatment protocols are needed. In addition, a combination of HBO treatment and particular chemotherapeutic agents (doxorubicin, bleomycin, and disulfiram) may cause potential toxicity[98] because it can potentiate oxygen-related serious organ damage.[99–101] However, studies showing conflicting results also exist.[102,103]

Role of hyperoxic treatment in radiation therapy

The primary mechanism of radiation therapy is creation of ROS, which in turn induces cell death by the mechanisms including apoptosis, necrosis, autophagy, and senescence.[104] In hypoxic state, DNA radicals are repaired by abstracting hydrogen from sulfhydryl group present in protein.[1] Since oxygen is required for ROS generation, hypoxic tumors are resistant to the cytotoxic effects of radiotherapy.[105] HIF-1 plays a role in radioresistance of a tumor by up-regulating downstream genes, which are involved in apoptosis, metabolism, proliferation, and neovascularization.[106] In general, cells irradiated under normal oxygenated conditions are two- to three-fold more radiosensitive than cells irradiated under hypoxic or anoxic conditions.[107,108] Several human studies reported significant improvement of survival and local tumor control in patients with cancer treated with radiotherapy and HBO.[109–111] However, other studies suggest a high rate of complications from combination of HBO and radiotherapy, including severe tissue radiation injury and seizures.[34,110] Concerning this matter, beneficial effects of NBO on tumor radiosensitivity have been also reported.[112,113] In addition, both the extent and the timing of this hyperoxic therapy are variable. From systematic reviews in patients with high grade gliomas, radiation therapy after HBO treatment was tolerated and beneficial.[111]

Role of hyperoxic treatment in immunotherapy

Oxygen tension directly affects immune cell function, and thus hypoxia can cause immunosuppression and/or immune dysfunction.[114] It is widely appreciated that hypoxic tumor microenvironment negatively affects anti-tumor immune responses, and also is responsible for resistance to immunotherapy.[16,115] Many mechanisms underlying hypoxia-induced immunomodulation in cancer have been suggested.[116] Extracellular adenosine, a potent immunosuppressive metabolite, is increased in hypoxic conditions, and controlled by two cell surface nucleotidases; CD39 and CD73 in tumors,[117,118] providing evidence that the adenosine-dependent immunoregulation is important for hypoxia-mediated immunosuppression. TGF-β, a potent immunosuppressive cytokine, is upregulated in tumor cells after culturing in hypoxic conditions.[119] Hypoxia also increases the accumulation of intracellular adenosine by HIF-1α-dependent mechanism, resulting in the elevation of extracellular adenosine independent of CD39/CD73.[120,121] Programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1), important players in immune checkpoint pathways, are also regulated oxygen-dependently in the tumor microenvironment. Hypoxia increases PD-L1 expression which induces cancer cell resistance to T-cell dependent cytotoxicity.[122,123]Exposure to adenosine or the activation of its receptors in T cells also downregulates T cell activities by inducing PD-1 and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) expression.[124,125] Activities of myeloid-derived suppressor cells (MDSCs), typical immunosuppressive cells in the tumor microenvironment, are also regulated by hypoxia and extracellular adenosine.[126,127]

Based on these findings, hyperoxia therapy has been attempted to restore hypoxia-induced impairment of immune function in cancer cells, in particular by downregulation of immune checkpoint pathways.[31] In mice, 60% oxygen efficiently reduced tumor burden only in wild-type mice, but not in immunocompromised mice, indicating the involvement of immune response in anti-tumor activities of hyperoxia.[31] Hyperoxia-induced alleviation of hypoxia reduces the levels of immunosuppressive molecules such as adenosine, TGF-β and PD-L1 in the tumor, and enhances anti-tumor immune responses.[31,58,59] Population of typical immunosuppressive immune cells such as MDSCs and Treg cells in the tumor microenvironment is also decreased by hyperoxia therapy.[20,31] Recently, Wang *et al.*[59] reported that hyperoxia reduces stemness of colorectal cancer cells through the inhibition of hypoxia-mediated production of exosome from granulocytic MDSCs.

The role of cancer immunotherapy has become increasingly important compared to traditional cancer treatments. Accumulating evidence indicates that attenuation of immunosuppressive activity in the tumor microenvironment by regulating immune checkpoints is the key factor for the success of cancer immunotherapy.[128] In this regard, it is intriguing that the inhibition of immune checkpoints pathways is the main mechanism underlying anti-tumor activity of hyperoxia.[114] Although several immune regulators and molecular mechanisms involved in hyperoxia-mediated antitumor activities have been identified, precise adjunctive role for hyperoxia in cancer immunotherapy still remains unclear.

Future directions and conclusion

Tumor hypoxia is a major treatment target for effective cancer therapy and inhibition of cancer progression. Hyperoxia therapy has been suggested to reverse cancer hypoxia, and it is more often used as an adjunctive treatment for cancer treatment along with other therapeutic modalities. Currently, no standard protocols for hyperoxic tumor therapy are approved. In case of combining hyperoxia with radiation, hyperoxic periods are relatively short and may not have significant side effects,[34] but in other cases where oxygen is administered over a long period, hyperoxia can cause cellular injury and organ dysfunction. Further, randomized, large, and well-organized clinical research could reinforce the use of hyperoxia therapy in the clinical setting for cancer treatment with minimal complications. Furthermore, more personalized approach according to the type of cancer and comorbidities are needed. Hypoxia-activated prodrugs or HIF inhibitors are suggested as possible alternatives to hyperoxic cancer therapy. The number of preclinical and clinical trials targeting low-oxygen tumor compartments via hypoxia-activated prodrugs is increasing.[129] In addition, combinations of clinical immunotherapy and immunomodulation from HIF inhibitor have a possibility of being powerful treatment option.[130] In conclusion, overcoming tumor hypoxia is an urgent problem to be solved for effective treatment of cancer patients. Further research is required to determine the mechanism for the role of oxygen tension in cancer progress and treatment, and to develop standard protocols for increasing efficacies and safety of hyperoxia therapy in cancer.

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