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Editorial

Hyperbaric oxygen: A potential new therapy for leukemia?

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Hyperbaric oxygen (HBO_2) therapy is the administration of 100%-inhaled oxygen to patients at increased atmospheric pressure. The amount of oxygen bound to circulating hemoglobin is very similar whether a patient breathes air at sea level or breathes 100% oxygen at increased pressure. In contrast, while the partial pressure of oxygen dissolved in plasma is usually 100 mm Hg in a person breathing air at sea level, it can exceed 1000 mm Hg in a person during an HBO_2 treatment. Consequently, HBO_2 enhances oxygen delivery to cells throughout the body. HBO_2 is a proven, effective treatment for patients with carbon monoxide poisoning, decompression sickness, and arterial air embolism. There is also evidence supporting the use of HBO_2 to treat gas gangrene, osteomyelitis, radiation tissue damage, and compromised skin grafts as well as to enhance the healing of selected problem wounds [1].

Oxygen is a potential anticancer therapeutic. Mammalian cells require oxygen to proliferate and, under certain conditions, cells also need oxygen to undergo apoptosis. In cancer, the balance between cell proliferation and apoptosis is not in equilibrium. Due to their rapid growth and limited angiogenesis, solid tumors have areas where oxygen concentrations are very low. While hypoxia probably slows tumor growth, it also causes these tumors to be resistant to the tumoricidal effects of radiation. Based upon these observations, HBO_2 was used successfully over 30 years ago as a radiosensitizer in clinical trials of head and neck cancer [2] and cervical cancer [3] performed by the British Medical Research Council. In vitro studies have demonstrated that HBO_2 can also increase the tumoricidal effects of chemotherapeutic agents [4]. Due to the cumbersome nature of administering chemotherapy and especially radiation to patients in hyperbaric chambers, HBO_2 therapy for cancer may have been prematurely abandoned.

Cells use oxygen as a terminal electron acceptor in the process of generating ATP in their mitochondria. Reactive oxygen species (ROS) are promiscuous byproducts of this reaction. When ROS react with macromolecules (such as proteins, lipids, and DNA), the initial reaction generates a second radical, which then reacts with another macromolecule, creating a radical-forming cascade. The overall balance between intracellular ROS production and antioxidant defense mechanisms determines the redox status of a cell. By increasing the amount of oxygen dissolved in the extracellular space both in vitro and in vivo, hyperoxia at ambient pressure and HBO_2 enhances intracellular oxygen levels and ROS [5]. The resulting milieu can cause the intracellular oxidative activities to overwhelm the reducing equivalents, thereby placing cells in a state of oxidative stress and activating stress signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway [6]. Although the molecular mechanisms whereby ROS induce these pathways are still uncertain, activating these pathways results in apoptosis. While hyperoxia and HBO_2 usually exert similar effects, in some models their effects differ, suggesting that increasing atmospheric pressure does more than simply further enhancing hyperoxia.

In this issue of Leukemia Research, Chen et al. report that HBO_2 induces apoptosis in the Jurkat T-cell leukemia and the NCI-H929 myeloma cell lines [7]. These findings confirm our earlier report demonstrating that HBO_2 induces spontaneous, radiation-induced, and chemotherapy-induced apoptosis in Jurkat and HL-60 promyelocytic leukemia cells [8]. These experiments demonstrate that HBO_2 is pro-apoptotic in hematopoietic cells, a phenomenon that merits confirmation in other leukemia cell lines. In contrast to the hematopoietic cell lines, neither Chen et al. nor our group were able to show that HBO_2 affects apoptosis in the non-hematopoietic A549 lung carcinoma and MCF-7 breast adenocarcinoma cell lines and in patient-derived benign and malignant mammary epithelial cells immortalized by transfection with the human papilloma virus E6 oncogene [9]. The molecular correlate of these cellular phenomena is Chen's intriguing observation that HBO_2 activates the pro-apoptotic MAPK pathway in hematopoietic cells, but not in non-hematopoietic cells.

In addition to stimulating apoptosis, oxidative stress can also trigger anti-apoptotic pathways. Not unexpectedly, Chen et al. observed that the anti-apoptotic ERK pathway is

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down-regulated or unaffected in HBO_2-exposed hematopoietic cells. While this group did not explore the status of ERK in HBO_2-exposed non-hematopoietic cells, Lee et al. have reported that HBO_2 activates ERK in human umbilical vein endothelial cells [10]. In addition, it is notable that oxidative stress turns on calcium/calmodulin-dependent kinases (and thereby ERK) [11] and that H_2O_2 induces MCF-7 cell apoptosis only if the cells are incubated in the presence of a calcium/calmodulin-dependent kinase inhibitor [12].

In addition to influencing apoptosis, HBO_2 can also affect cell proliferation. HBO_2 inhibits proliferation in some models and stimulates it in others. Studies showing HBO_2's antiproliferative effects led to the aforementioned 1970s clinical studies showing that HBO_2 slowed tumor progression. However, because HBO_2 enhances proliferation in some in vitro models, there are also concerns that HBO_2 could promote cancer progression in vivo [13]. To address this possibility, Feldmeier et al. reviewed human and animal studies examining the effect of HBO_2 on tumor progression [14]. These authors concluded that HBO_2 treatment has a neutral effect on solid tumor growth. There were an insufficient number of studies available for them to reach any conclusions regarding the in vivo effects of HBO_2 on hematopoietic cancers.

The effects of HBO_2 on cellular function are also influenced by the extracellular environment. Because HBO_2 produces much higher oxygen tensions in cell culture media than in vivo, it is possible that HBO_2's effects on apoptosis and proliferation are in vitro phenomena. For this reason, human primary leukemia cells should be transplanted into immunodeficient mice, the mice exposed to HBO_2, and apoptosis measured. If HBO_2 causes leukemia cell apoptosis in these animal models, primary human leukemia cells could then be exposed to HBO_2 ex vivo, and the cell death pathways further studied to provide more insight into how HBO_2 might be used against leukemias.

In summary, the finding that HBO_2 promotes leukemia cell apoptosis prompts us to reconsider using HBO_2 to treat cancer. Because it suppresses proliferation, HBO_2 has been used to treat solid tumors. Because it promotes apoptosis, HBO_2 merits further study as a novel treatment for leukemias, either alone or as an adjuvant to chemotherapy.

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