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Hyperbaric Oxygen Therapy as Adjuvant Therapy in Nasopharyngeal Cancer : A Literature Review

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Introduction

Hyperbaric oxygen therapy (HBOT) may not be widely known. In Indonesia itself, the HBOT application was first carried out in 1960 by the Indonesian Navy Marine Health Institute / Lembaga Kesehatan Kelautan TNI AL (Lakesla) in collaboration with the Naval Central Hospital (Rumah Sakit Pusat Angkatan Laut / RSPAL) Dr. Ramelan Surabaya, where until now the facility is still the largest in Indonesia. Hyperbaric oxygen therapy was first introduced by Behnke in 1930. At that time hyperbaric oxygen therapy was only given to divers to relieve symptoms of decompression sickness (Caisson's Disease)[1]. Hyperbaric oxygen therapy is a treatment method using high pressure oxygen, where the pressure used is higher than atmospheric pressure (more than 1 atm). High pressure oxygen therapy methods are currently widely used as adjuvant therapy for various pathological conditions associated with hypoxic and/or ischemic conditions. The standard procedure for HBOT is to inhale pure oxygen (100% O_2) using a pressure between 1.5 and 2.5 atmospheres absolute (ATA) by mask or by endotracheal tube which is the sum of the atmospheric pressure and the gauge pressure in a hyperbaric chamber[2–4].

Oxygen is delivered in the blood to the tissues mostly through its binding with hemoglobin (Hb) molecules in red blood cells (erythrocytes) and a small amount is dissolved in blood plasma. At normal atmospheric pressure, 97% of the hemoglobin in the body is bound to oxygen. While oxygen dissolved in plasma is usually only 0.32%. Based on this term, therapeutic management of HBOT will not have a major effect on oxygen delivery through red blood cells, but may increase hemoglobin-independent delivery through plasma. The basis of hyperbaric therapy contains physics principles. Toricelli theory that underlies the therapy used to determine the air pressure of

1 atm is 760 mmHg. The composition of the air contains 79% Nitrogen (N_2) and 21% Oxygen (O_2), equal in our breathing system. In hyperbaric oxygen therapy chamber contains 100% Oxygen (O_2). Hyperbaric therapy is also based on the basic physical theory of the laws of Dalton, Boyle, Charles and Henry. While the principle adopted physiologically is that the absence of O_2 at the cellular level will cause disruption of life in all organisms. Oxygen that surrounds the human body enters the body through gas exchange. The respiratory phases of gas exchange consist of ventilation, transport, utilization and diffusion phases. With conditions of high pressurize oxygen, it is hoped that the cellular matrix that supports the life of an organism will get optimal conditions.

Cancerous region often contain acute or chronic hypoxia areas in different severity according tumor types and patients condition. Cancer cells can survive and grow in the host because they have adaptaion capability in the hypoxic microenvironment. Hypoxia environtment within cancer area caused by the functional and structural abnormalities of the vascular network since oxygen demand of cancer growth overrides the adaptation ability of the cancer vasculature. In the past, hypoxia was thought to be a limiting factor of cancer growth by reducing the ability of cells to multiply. Currently, hypoxia is shown to be a causative factor in cancer development because the decrease of oxygen tension result for more malignant cells and induces multiple cellular adaptations, which sustains cancer progression and induces cancer growth. Hypoxia results in cellular responses which increase oxygenation and viability through stimulation of angiogenesis, metabolism alteration by increased glycolysis and upregulation of genes involved in cell survival or apoptosis.

Oxygen concentration has an important role in radiation oncology and radiation resistance. The transition from epithelial-to-mesenchymal cells in cancer induced by hypoxic conditions, result to cancers with an invasive or metastatic phenotype. Given its crucial role as a negative prognostic and predictive factor, hypoxia is considered as one of the best targets in cancer treatment. This oxygen role leads to the question will lack of oxygen inhibit cancer progression, or is hyperoxygenating the tumor tissue the way to go in order to prevent cancer growth and development.

This review explaines the medical use of HBOT in the treatment of cancer, with a

particular focus on the use of HBOT as an adjuvant therapy of nasopharyngeal cancer.

Hyperbaric Oxygen Therapy and The Cancer

Angiogenesis is one of the important factors in the cancer growth and metastasis. Hyperbaric oxygen therapy increases cellular and vascular proliferation in normal and injured tissues, so it is hypothesized that HBOT may also induce angiogenesis in cancer. Studies on two rats mammary tumor models and one glioma model obtained different results from the literature hypothesis. HBOT induces antiangiogenic effects in mammary tumor models and does not affect angiogenesis in glioma models[5–7]. In his review, Moen et al. discusse about tumor angiogenesis and oxygen tissue perfusion, underlining the difference between cancer tissue and wounds and concluded that HBOT is not cause tumor angiogenesis enhancement[8]. Asfar said that there is important to distinguish between normal or injured tissue and tumor tissue because lack of evidence that HBOT enhanced angiogenesis in cancerous tissue[9].

Metastasis is a complex process consisting of local invasion of tumor cells, entry into blood or lymph vessels, and re-penetration and colonization at distant sites. Angiogenesis is also required for distant metastases to occur[10]. Studies that examine the relationship of hyperbaric oxygen therapy with the occurrence of metastases in cancer are still very limited. In the several observational studies conducted on the effect of HBOT on the metastatic process, none of the studies demonstrated induced metastasis after HBOT[11,12]. Of course, more studies are needed that discuss the relationship of metastasis with HBOT.

Prolonged hyperoxia in the body can increase levels of reactive oxygen species (ROS), overwhelm antioxidants and cause cellular damage and possibly organ dysfunction. The tissue damage that occurs depends on the type of cell, oxygen concentration, and exposure. There are few studies on the occurrence of apoptosis in neoplasms receiving HBOT therapy. Studies in breast and head and neck cancer have not shown any change in apoptosis for HBOT therapy[13,14]. In a study conducted by Chen et al. We found pro-apoptotic mitogen-activation protein kinase (MAPK) pathway activation and downregulation of the anti-apoptotic ERK pathway in hematopoietic cells after HBOT. In two animal model studies with gliomas and mammary tumors there was induction of cell death after HBO treatment. Proliferation cell reduction together with a significant histological

alteration, has also been shown after HBO treatment in dimethyl benz-antrachene (DMBA)-induced mammary tumors. In addition, cell studies of osteosarcoma and nasopharyngeal carcinoma supported the support of cell division after HBO treatment. From some of these studies it can be said that changes in oxygen concentration can affect antioxidant pathways that lead to desired changes in cell life[5,6].

Hyperbaric Oxygen Therapy and Cancer Treatment

Hypoxia is one of the important factors in the occurrence of chemotherapy resistance. Chemoresistance associated with hypoxia is caused by a decrease in drug cytotoxicity that causes in cellular metabolism alteration, the formation of ROS due to prolonged hyperoxia which causes a significant increase in cytotoxicity, and genetic instability that causes cell resistance to drugs. ROS are formed as a result of oxidative stress in eukaryotic cells and are triggered by a lack or excess of oxygen levels in the tissues, radiation, toxins, or by other adverse factors. ROS cause cell damage through oxidation that results in DNA strand breakage, apoptosis, and cell death. Hypothesis Al-Waili et al. In his paper on the potential role of HBOT in combination with conventional therapy, HBOT can enhance and help overcome chemotherapy resistance by increasing tumor perfusion and cellular sensitivity[8]. Clinical studies conducted by Hei et al. Regarding the effect of HBOT on chemotherapy, HBOT is placed as the initial treatment to increase vascularity in order to increase the effect of chemotherapy[11]. The results of the study stated that HBOT did not increase neovascularity and the potentiation of HBOT to chemotherapy was not significant. Nasopharyngeal carcinoma (NPC) is a head and neck malignancy arising from the nasopharyngeal epithelium with a high incidence in Southeast Asia and southern China. NPC itself is a tumor that is very sensitive to radio and chemotherapy. For stage I and II NPC (according to the UICC/AJCC staging system), radiotherapy is a routine treatment that can provide a good prognosis. For stage III–IVA NPC, the main treatment is a combination of chemotherapy and radiotherapy. Cisplatin-based chemotherapy is the standard treatment for stage III–IV NPC. For recurrent and metastatic NPC, the clinical response to radio and cisplatin-based chemotherapy was not satisfactory[15,16]. The platinum-containing regimens of cisplatin and fluorouracil are the first-line therapy in recurrent NPC resulting in a therapeutic response rate of 40–65%.

Several other drugs used in NPC metastases are Carboplatin, Doxorubicin, Epirubicin, Paclitaxel, Docetaxel, Gemcitabine, Bleomycin, and Methotrexate[17]. The study conducted by Firm et al. In NPC, there was an increase in the response to chemotherapy during and immediately after HBOT therapy. Based on the results of this study it can be concluded that potentiation with chemotherapy cannot occur unless the chemotherapeutic agent is administered during or immediately after the HBOT session, i.e. when the pO2 increases[15]. The study of Moen et al. in breast tumors treated with 5-FU found an increase in the absorption of chemotherapy drugs in DMBA-induced tumors after HBOT[8]. While the combination of HBOT and chemotherapy as a therapeutic modality in other types of cancer provides a prolongation of the effectiveness of carboplatin in glioma patients in a mouse model[18]. Li et al. examined the effect of cisplatin treatment in combination with HBOT on NPC in a mouse model, it was found that tumor growth reduction was more effective than single cisplatin therapy[19]. Kawasoe et al. found that both in vivo and in vitro, HBOT enhances the chemotherapeutic effect of carboplatin in osteosarcoma[20]. However, Mayer et al. in his study listed five chemotherapeutic agents (doxorubicin, bleomycin, disulfiram, cisplatin, and mafenide acetate) that were contradictory when combined with HBOT because of their potential toxicity[21]. Research on combination chemotherapy other than cisplatin and fluorouracil and HBOT is still rare. Linking knowledge about different chemotherapy in relation to cancer subtypes is important for further study and development of NPC therapies and adjuvants.

The mechanism of action principles of radiotherapy is through the classical oxygen effects in the treatment of tumors. Upon exposure to radiation, water molecules undergo radiolysis to form hydrogen and unstable hydroxyl radicals. This causes serious DNA strand damage and consequently leads to cell death. From this mechanism, it can be said that radiotherapy works optimally on well-oxygenated tumor tissue[11,18,21,22].

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oxygenated tumor tissue[11,21–23]. HBOT in combination with radiotherapy may act as a radiosensitizer, enhancing the effects of radiation, or it may act as a therapeutic agent by reducing radiation injury. The combination of HBOT and radiotherapy reduces tumor growth and improves local tumor control, resulting in increased survival[21]. Mayer et al. conducted a clinical trial on 320 NPC patients who received a combination of radiotherapy and HBOT. The results showed that local tumor control and patient survival in the HBOT group were significantly better than the normobaric group[21]. HBOT eliminates the negative side effects of radiotherapy such as post-radiation tissue injury[15]. Similar results were obtained by Cade and McEwen in a study involving 505 patients with various types of cancer into a clinical trial that looked at the effects of combined HBOT with radiotherapy[24]. Hall et al. obtained similar results in a clinical trial of the treatment of head and neck cancer in which HBOT was used as a radiosensitizer. In this trial, survival time was not significantly different in the two treatment groups, but local tumor control increased in the HBOT group. In a further study, Hall et al. also observed significant improvements in patient survival (60 vs 30%) and local tumor control (63 vs 30%) on combined HBOT radiotherapy[23]. Several other study groups, conducting similar independent experiments, noted a high prevalence of severe late complications[16,18–21]. Another recent report showed that HBOT treatment of patients with head and neck cancer in addition to improving local tumor control, side effects caused by excessive radiation doses can also be reduced[15,23].

Hyperbaric Oxygen Therapy and Nasopharyngeal Cancer

Head and neck cancer was defined as neoplasma that origin from nasal cavity. Sinuses, lips, throat, or laryngx according to The National Cancer Institute[25]. A few study has been done during recent years, where HBOT has been studied in combination with radiotherapy in mice carcinoma model of nasopharyngeal carcinoma. They found that HBOT reduce the hypoxic state of the tumors region, otherwise it did not have any effect on tumor growth, neither alone nor in combination with radiotherapy[15,17,19]. The researchers did not find any evidence of angiogenesis enhancement in the tumors after HBOT treatment. This study supports the notion that HBOT does not induce tumors angiogenesis[6]. Teguh et al. reviewed the effect of combining HBOT with radiotherapy. A significant difference was

observed between the nonHBOT vs. HBOT groups in almost every quality of life (QoL) issue studied. They emphasize the potential beneficial effect of early hyperbaric oxygen. Several issues remain to be explored. It is of interest to determine the optimal commencement of HBOT after radiation therapy as well as the necessary number of treatments. Also, the mechanisms through which HBOT shortly after radiotherapy cause the demonstrated beneficial effects on QoL should be further explored. Because questions remain regarding HBOT after radiotherapy, a bigger randomized trial should be conducted to answer the remaining questions[15,26]. Many studies have shown beneficial results on local tumor control, mortality, and local tumor recurrence, in HBOT group. However, the conclusion within the field of HBOT and radiosensitization has not yet reached a consensus.

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