Hyperbaric oxygen therapy in the treatment of complications of irradiation in head and neck area.

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Narozny W, Sicko Z, Kot J, Stankiewicz C, Przewozny T, Kuczkowski J. Hyperbaric oxygen therapy in the treatment of complications of irradiation in head and neck area. Undersea Hyperb Med; 32(2):103-110. Background and purpose: We have investigated the treatment results of hyperbaric oxygen (HBO_2) to patients with radiation-induced tissue complications. Material and methods: Eight patients (1.4%) from 548 with head and neck cancers treated surgically with post- or preoperative radiotherapy or radiotherapy alone in standard doses who developed postradiation complications (6 patients with laryngeal chondroradionecrosis, 1 patient with osteoradionecrosis of the temporal bone, and 1 patient with soft tissue radionecrosis) are presented. To evaluate radiation reactions occuring in the head and neck region, we used the Chandler grading system for classification of postradiation larynx injuries and SOMA/LENT score for classification of postradiation injuries of mucosa of upper aerodigestive tract. Grades I and II in those grading systems are expected side effects of radiation therapy, thus our cases were all in grades III and IV. The HBO_2 was performed after failure of the conventional treatment (antibiotics, steroids, topical therapy). The number of HBO_2 expositions was from 8 to 39 and the delay to therapy from 2 to 22 months. Results: Symptoms resolved in all treated patients. Six patients with laryngeal chondroradionecrosis had no symptoms after therapy and in three of them after partial laryngectomy the decannulation was performed. In one patient with mucosal radionecrosis after total laryngectomy, the esophageal fistula was closed and in one patient with osteoradionecrosis of the temporal bone, wound debridement followed. Conclusion: The authors' experience supports the increasing clinical evidence that HBO_2 is an effective adjunct therapy for treatment of complications of irradiation in head and neck area.

INTRODUCTION

Radiotherapy is an effective treatment for malignancy, but it is not free from adverse effects. It destroys tumor cells but it also affects normal tissues located in the irradiated area. Radiation has been shown to produce atrophy, necrosis, ulceration, metaplasia, and sometimes carcinogenesis in epithelium and interstitial tissue; fibrosis, necrosis and exudation in interstitium; exfoliation of the endothelial cells, thrombosis and microembolism in the blood vessels (1,2).

In the final stage, tissues are hypovascular, hypocellular and hypoxic (named "3H" by Marx). The oxygen partial pressure in irradiated tissue decreases significantly, sometimes to 5–10 mmHg. The clinical features include swelling, ulceration, necrosis, increased susceptibility to infections, and poor wound healing (3).

Clinical features of radiation-induced tissue injury of head and neck can vary from hyperemia and swelling of the mucosa or skin (low-grade radiation injury) to post-radiation complications of soft tissue radionecrosis,

chondroradionecrosis and osteoradionecrosis (1-4, 7). The level of tissue injury depends on several factors including type and energy of radiation, total radiation dose, number of radiation fractions, and dose per fraction, susceptibility of irradiated tissues, oxygen tension and level of hydration in irradiated area. The time between the last dose of radiation and evident tissue injuries depends on the rates of many biological processes that run from a few seconds to many years (5-7). In the very first phase after the irradiation of the normal tissue the damage to small blood vessels and connective tissues is dominant. Later on, some recovery from acute damage can be observed, but there may be signs of permanent tissue damage and replacement fibrosis. In intermediate phase degenerative changes in microvascularity and interstitial fibrosis may progress slowly, and in the chronic phase a delayed parenchymal degeneration can lead to the necrosis of the tissues (8). Using clinical observations the concept of tolerance-dose was developed. It represents estimates at which, for a given treatment, a certain percentage of all patients will develop specified normal tissue damage of a specified grade in a specified time period. It was assumed that it is a dose which – after standard fractioning method 2 Gy / day for 5 days a week - leads to 5% of late-occurring normal tissue damage during 5 years of observation. Example tolerance doses are 60 Gy for mandible (osteoradionecrosis), 70 Gy for larynx (chondroradionecrosis), and 32 Gy for salivary glands (xerostomia) (5). The rate of post-radiation reactions in head and neck differs as depending which clinical feature is analyzed. It is higher in edema, and lower in osteonecrosis, chrondronecrosis, or soft-tissue necrosis.

Based on the literature, Pasquier noted a 1– 37.5% incidence of osteoradionecrosis after radiation therapy due to carcinoma of head and neck (9). Chondroradionecrosis is an uncommon complication of radiotherapy of the head and neck; it occurs in 1% of irradiated patients if daily dose is 2 Gy, and total dose is 70 Gy (4, 7, 9, 11). There are some risk factors which can increase this rate, including hypofractionating, increasing the total dose, extending the field size, and direct cartilage infiltration by tumor (4, 12, 13). Laryngeal radionecrosis can occur if larynx is included in the radiation field during treatment of tongue or tonsillar carcinoma (1, 5, 6, 11, 12). The vast majority of patients who develop laryngeal radionecrosis present with these symptoms within 1 year of treatment; however, delayed presentations have been reported up to 53 years after radiotherapy (14). Chondroradionecrosis of the larynx is still a diagnostic dilemma as it may be very difficult to differentiate between persistent or recurrent tumor and severe radiation effects (15). Keene et al (13) reported chondroradionecrosis of the larynx by histological examination of specimens taken from edematous mucosa with suspected recurrence of carcinoma. The reported incidence rate of post-radiation soft-tissue necrosis ranges from 1 to 18% of irradiated patients and depends on technique of radiation (generally it is higher for brachytherapy than for conventional radiation) (9).

Prolonged healing of wounds after surgical treatment of carcinoma of head and neck can be caused by radiation of tissues previously affected by concomitant disturbances: metabolic (diabetes mellitus), infectious, toxic (drug induced), vascular, neurological, traumatic (burning, frostbite) (10, 14, 17).

A system for classification of post-radiation injuries is necessary for planning the therapy and assessing its efficacy, as well as for exchange of clinical and scientific data. Chandler's grading system from 1979 is a

generally accepted guide for classification of post-radiation larynx injuries (4). The SOMA-LENT scores created by RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) are used for classification of post-radiation injuries of mucosa of the upper aerodigestive tract (18).

MATERIAL AND METHODS

The period for this retrospective study was between January 1, 1998 and December 31, 2002 when the ENT Department of the Medical University of Gdansk treated 811 patients with head and neck cancer. In 548 patients, post- and pre-operative radiotherapy or radiotherapy alone was applied. An evaluation of radiation reactions occurring head and neck tissues was done according to the Chandler's or SOMA/LENT classifications. Grades I and II in those classifications are expected side effects of radiation therapy delivered in therapeutic amounts to this region whether or not it is the site of the lesion receiving treatment. Grades III and IV are complications (4, 18). In our department we observed post-radiation complications in 15 patients (2.7%). Seven of them (1.3%) were successfully treated by a conventional treatment (antibiotics, steroids, inhalations, swabbing of the oral mucosa, etc.), but clinical failure was observed in other 8 patients (1.4%) treated by the same methods. Those 8 patients were primarily treated for carcinoma of the larynx (4 patients), carcinoma of the palatine tonsil (3 patients), and carcinoma of the temporal bone (1 patient). The reference doses of 60-66 Gy in 30-33 fractions were administered using a ^{60}Co machine. Additionally in 5 cases 18-20 Gy electron beam dose was given to the posterior neck lymph nodes.

Subjects with post-radiation complications in the late phase (more than 2 months from exposure) were admitted for hyperbaric oxygen therapy with attention to absolute and relative contraindications after Jain (10). Before HBO_2 the general and laryngological examination was conducted, as well as neurological or ophthalmological examination if necessary. All patients had a chest X-ray and spirometry if the X-ray was abnormal.

HBO_2 therapy was conducted in the National Center for Hyperbaric Medicine in Gdynia. All patients in the HBO_2 group received 100% oxygen in a multiplace chamber under pressure of 2.5 ATA for 60 minutes (plus two 5 minutes air breaks), once daily, five days a week. The pressure inside the hyperbaric chamber was achieved by compressed air. Patients breathed 100% oxygen from tight systems in order to avoid leakage of oxygen into the chamber. The exhalation was directed outside the chamber using a dump valve system in order to keep the fraction of oxygen below 23% for fire safety. The total number of sessions depended on clinical status. The median number of HBO_2 sessions was 18 and ranged from 8 to 39.

Clinical criteria for positive outcome included resolution of hoarseness with dyspnea, odyno- and/or dysphagia with complete restoration of movement of vocal fold visualized by indirect or direct laryngoscopy for patients with post-radiation complications in larynx, and absence of bacterial infection of wound (confirmed by at least 3 negative microbiological smears) in patients with post-radiation complications in soft tissues.

RESULTS

The results are summarized in Table 1.

There were 5 males and 3 females in our treatment group ranging in age from 38 to

Table 1. Patients and treatment results.

No.	Gender / age [years]	Primary diagnosis TNM	Primary treatment	Indication for HBO_2	Number of HBO_2 sessions / delay to start of HBO_2	HBO_2 effect	Oncological effect / time (months)
1	F/59	TC $T_3N_2M_0$	T + ND1, RT (^{60}C 60 Gy; electron beam 20 Gy)	CRN Chandler's Grade III	17/6	C	NEC/60
2	F/52	TC $T_2N_2M_0$	T + ND1, RT (^{60}C 60 Gy; electron beam 20 Gy)	CRN Chandler's Grade III	15/2	C	NEC/42
3	M/56	TC $T_3N_2M_0$	ND1, RT (^{60}C 66 Gy; electron beam 18 Gy)	CRN Chandler's Grade III	20/22	C	NEC/25
4	M/54	LC $T_2N_2M_0$	PL, RT (^{60}C 60 Gy)	CRN Chandler's Grade III	20/6	C Decannulation	NEC/48
5	M/50	LC $T_2N_0M_0$	PL + ND2, RT (^{60}C 66 Gy; electron beam 20 Gy)	CRN Chandler's Grade III	8/5	C Decannulation	NEC/42
6	M/45	LC $T_2N_0M_0$	PL + ND2, RT (^{60}C 66 Gy; electron beam 20 Gy)	CRN Chandler's Grade IV	16/13	C Decannulation	NEC/48
7	M/52	LHC $T_4N_3M_0$	RT (^{60}C 66 Gy), TL + ND1	MRN Grade IV (SOMA-LENT)	39/3	Closing of the esophageal fistula	NEC/18
8	F/38	TBC $T_4N_0M_0$	RT (^{60}C 66 Gy)	ORN Grade IV (SOMA-LENT)	19/4	Wound debridement	RC/4

Abbreviations: TC – tonsil carcinoma; LC – laryngeal carcinoma; LHC – laryngeal and hypopharyngeal carcinoma; TBC – temporal bone carcinoma; T - tonsillectomy; PL – partial laryngectomy; TL – total laryngectomy; ND1 – unilateral neck dissection; ND2 – bilateral neck dissection; RT – radiotherapy; CRN - chondroradionecrosis; ORN - osteoradionecrosis; MRN – mucosal radionecrosis; C - cured; NEC – no evidence of carcinoma; RC – recurrence of carcinoma

59 years (mean 51.1±7.2[SD]). It is worthwhile to notice that in 3 cases (patients 1 to 3 in Table 1) treated by surgical interventions with postoperative irradiation because of the tonsil carcinoma, the post-radiation injuries were diagnosed in larynx which was not affected by primary disease, but was only located in the radiation field. All of them were scored as grade III in Chandler's classification. They complained of hoarseness with dyspnea, odyno- and dysphagia associated with uni- or bilateral vocal fold immobility, significant laryngeal edema, and skin involvement. In two female cases the complication occurred 2 and 6 months after radiation and in one male case after 22 months after completion of radiotherapy. Interestingly, in our experience chondroradiation necrosis of the larynx was more common in women. This finding is even more striking since many fewer women have head and neck cancers and many fewer receive radiation. Complete cure was observed for all those patients after 15 to 20 HBO_2 sessions and in 25 to 60 months of follow-up observation no evidence of carcinoma recurrence was observed.

The second group consisted of 3 males ranging in age from 45 to 54 years with larynx carcinoma staged T2 (cases 4 – 6 in Table 1). They were treated by partial laryngectomy (supraglottic), and the treatment was extended by bilateral neck dissection in two cases with radiotherapy. In all of them, chondroradionecrosis was classified as Chandler's Grade III and IV. They complained of pain, swallowing difficulties, loss of taste, dyspnea, and over a 10% loss of body weight. There were deep ulcerations of the mucosa with exposure of laryngeal cartilage. All patients had tracheotomy because of dyspnea. The time delay between completion of therapy and complication occurrence was 5 to 13 months. Patients participated in 8 to 20 HBO_2 sessions. The symptoms disappeared, larynx changes resolved, and decannulation was possible in all cases. During 42 to 48 months of follow-up, no evidence of recurrent carcinoma was observed.

There was one case of male with carcinoma of larynx and hypopharynx (case 7 in Table 1). He had been primarily irradiated, and then total laryngectomy with unilateral neck dissection was performed. Three months after completion of therapy he had laryngopharyngeal fistula with mucosal necrosis of the hypopharynx and oesophagus (grade IV SOMA-LENT). Moreover, a mixed infection occurred, and aerobic and anaerobic bacteria were isolated from the wound (*Prevotella melaninogenica*, *Peptostreptococcus* sp., *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Enterococcus faecalis*). After 39 HBO_2 sessions no more anaerobes were isolated, and the fistula was closed by a pedicle musculocutaneous flap. There were 18 months of follow-up.

There was one case of 38-year-old female (case 8 in Table 1) with extensive carcinoma of the temporal bone treated by radiation. Four months after completion of radiotherapy osteoradionecrosis occurred with sequestration and total destruction of external, middle and internal ear. After 19 HBO_2 sessions a complete debridement of the wound was achieved. The dura mater of the posterior fossa was exposed, but no leakage of cerebrospinal fluid was observed. After 4 months she had a local recurrence and died 14 months after initial diagnosis of the carcinoma.

DISCUSSION

The approved lists of indications for HBO_2 by the Undersea and Hyperbaric Medical Society and the European Committee for Hyperbaric Medicine are now widely accepted. Both include delayed radiation

injury of soft tissue and bone necrosis. This topic was discussed in detail during the Consensus Conference "Hyperbaric Oxygen Therapy in the Treatment of Radio-induced Lesions in Normal Tissues" of the European Society for Therapeutic Radiology and Oncology (ESTRO) and European Committee for Hyperbaric Medicine in Lisbon, Portugal in 2001 and reported by Pasquier (9).

In the 1970's the results of treatment of post-radiation injuries were unsatisfactory. The prolonged therapy of antibiotics, steroids, inhalations, progressive radical surgery was significant in decreasing the quality of life. Therefore new treatment options were sought, and HBO_2 introduced a new mechanism for repairing injured tissues. Greenwood et al. (19) first reported beneficial effects of HBO_2 in the treatment of chondroradionecrosis of the larynx in 1973, and Mainous et al. (20) in 1975 reported good results with HBO_2 treatment of osteoradionecrosis of mandible. The introduction of HBO_2 for treatment of post-radiation injuries dramatically improved the outcome of radiation injuries (10, 11, 21-24). HBO_2 administered prophylactically before surgical interventions in pre-irradiated patients, also decreased the incidence of postoperative infections by 4-5 fold and enhanced wound healing (25). HBO_2 offers considerable savings in the costs of national health care (treatment cost of osteoradionecrosis of the mandible is ~$140,000 in the USA), in this case by approximately 70%, regardless of indirect social benefits like decreasing absenteeism and increasing the quality of life (21, 24, 26).

HBO_2 is an efficient treatment of post-radiation tissue injuries, especially in the late phase, which takes months and is caused in large part by vascular damage leading to local hypoperfusion. Marx (27) reported his experience with 160 patients with head and neck cancer receiving HBO_2 in support of surgical resection or flap reconstruction in heavily irradiated patients. He compared wound infections, dehiscence and delayed healing. The rate of those complications was 4-5 times less in the group of patients treated with HBO_2 compared to patients not treated in hyperbaric chamber. Other authors, including Feldmeier et al, Ferguson et al, and Filintisis et al reported positive outcome in patients treated with HBO_2 for chondroradiation necrosis of the larynx showing that in more than 80% of cases it was possible to avoid the laryngectomy (28, 29, 30). An evidence-based approach to application of HBO_2 in prevention and treatment of delayed radiation injury by Feldmeier and Hampson reviewed 7 reports published before 2001 with 228 cases of soft tissue radiation necrosis of the head and neck including laryngeal necrosis (31). They concluded that according to the American Heart Association (AHA) therapeutic intervention classification (32) HBO_2 can be considered an AHA category IIb (acceptable and useful based on fair to good evidence), and according to the BMJ Clinical Evidence system (33) it would be rated "likely to be beneficial" based on the consistently positive outcome and low likelihood of substantial side effects. This conclusion is also supported by our own clinical observations.

HBO_2 is rarely used in Poland, probably because of the lack of general accessibility to hyperbaric centers. However, even in Italy, where there are more hyperbaric centers than in Poland, Marroni et al. (24) reported that HBO_2 is performed in only 12% of patients with mandiblar osteoradionecrosis, and in only 35% of patients with soft tissue radionecrosis. There is a strong need to improve the quality of life of those patients, as well as to decrease medical cost; therefore HBO_2 should be made available for the treatment of post-radiation complications.

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