



Re-Irradiation of Head and Neck Cancer: Possibilities of Cytoprotection

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Abstract

Background: For more than half a century re-irradiation has been used as salvage treatment of recurrent head and neck cancer with reported 24-month survival rates of 30-40%. Severe acute and late toxicities are observed in up to 50% of patients limiting quality of life. Amifostine is a well-studied selective cytoprotective agent available in clinical practice. Does amifostine represents an option to reduce toxicities in a re-irradiation setting?

Material and Methods: Data of three single centre studies with a total of 53 patients were pooled for evaluation, 42 patients received re-irradiation for head and neck cancer disease, 11 had pelvic tumors (rectal cancer n = 5, cervical cancer 2, endometrial cancer 2, uterus sarcoma 1, prostate cancer 1). All head and neck cancer patients concomitantly received chemotherapy for radiosensitizing.

Results: The combination of chemo- and radiotherapy were feasible in all patients pre-treated with Amifostine 500mg with a significant reduction of grade 3 and 4 toxicities. The cumulative doses were >110 Gy for both radiotherapy courses. Acute mucosal and skin toxicities (mucositis, stomatitis, diarrhea, dermatitis, cystitis, proctitis) were reduced to grade ^o1/2 level in 49/53 patients. Grade 3/4 toxicities were seen in only <10% (n=4). No objective data were available for late toxicities and survival.

Conclusion: Literature to date demonstrates the potential ability of amifostine to reduce the toxicity from re-irradiation in patients with recurrent head and neck cancer as well as a small number of pelvic tumors. Further research is suggested to confirm the cytoprotective benefits of amifostine in patients receiving re-irradiation for salvage treatment.

Keywords: Re-irradiation; Head neck cancer; Amifostine; Cytoprotection; Salvage; Radiosensitizing

Introduction

In 2014 Guntinas-Lichius “et al.” [1] had re-analyzed the Federal State Tumor Registry of Thuringia and reported a local recurrence rate of 16.5 % for cancer patients of the head and neck region (1040 recurrent diseases in 6291 cases between 1996 and 2011). The recurrent free survival rates were 68.8%–76.5% after 5 years [1]. Rescue surgery is usually reserved for patients with limited volume recurrent disease or development of second malignancies in a previously irradiated field. Re-irradiation is an option for those who are not suitable candidates for salvage surgery.

Re-Irradiation in Head and Neck Cancer Patients

In the late 1960's Wang published reports of re-irradiation in patients with limited volume larynx cancer recurrence in an attempt to preserve the larynx [2]. 30 years later the same author published his follow-up data in 20 patients. The 5-year-survival was 93% in stage I disease and 60% in stage II disease [3]. The idea of re-irradiation was extended to other ENT tumor localizations in the forthcoming years. Brachytherapy had been used as the first choice technique for recurrent diseases in the head and neck region. All researchers reported high local response rates (60-72%) with overall survival rates nearly 25% after 5 years. The main toxicity was soft tissue necrosis in a quarter of all treated patients [4,5]. In the late 90's the first meta-analysis was published analyzing the role of external beam radiotherapy. 3D conformal radiotherapy based on MRI/CT guided planning techniques had resulted in smaller and more precise target volumes. The majority of authors suggested that a 2nd radiotherapy course of >55 Gy was necessary to be curative. The main

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complication was trismus in 16-30% however the rate of soft tissue necrosis was decreased compared to brachytherapy use [6-8]. The overall rate of serious complications was 7%. Major risk factors for toxicity were early recurrent disease and older age of the patient [9]. All reviews and meta-analyses summarize the following key points for effectivity and toxicity: time interval between radiotherapy courses, total dose and target volume of radiotherapy. The 2-years survival is nearly 30%, grade 3 or 4 toxicities occurred in 30-40% of all patients [10,11]. In 1995 Harraf "et al." [12] introduced the idea of using concurrent radio-chemotherapy and observed better results than chemotherapy alone. Cisplatin, and 5-Fluorouracil are established radiosensitizers [12,13]. Modern approaches integrate EGFR-inhibitors such as Cetuximab with a moderate increase of toxicities for the patients [14].

Since 2002 different groups reported about their experiences with IMRT in the treatment of recurrent head and neck tumours. Chua "et al." [15] treated 31 patients with recurrent nasopharyngeal carcinoma and registered late toxicities in 70% of the patients, including ototoxicity and neuralgia in 19%. Lee "et al." [16] analyzed a large group of 105 patients who had received re-irradiation with IMRT and reported serious acute toxicities in 23% and serious late toxicities in 15% [16]. Other authors have seen late toxicities in up to 35% of patients [17,18].

Cytoprotection as Supportive Concept in Head and Neck Oncology

Free radicals generated by ionizing radiation are responsible for the efficacy and toxicity of radiotherapy. Head and neck cancer patients frequently using trace elements or vitamins to act as scavengers of free radicals in order to reduce the toxicities that occur during and after the therapy [19]. Amifostine was developed by the US Army Medical Research and Development Command to protect civilians and soldiers against radiation from a nuclear explosion. Subsequently it was the first drug used clinically for protection from Xerostomia caused by standard radiotherapy [20]. Tumor cells have lower concentrations of membrane bound alkaline phosphatase which is necessary to change the prodrug Amifostine to its active free-radical scavenging form, WR-1065. The resulting diversity between reactions in tumor tissue and normal tissue is the ideal base for its pharmacological activity as supportive agent [21]. Amifostine's market approval was based on a study performed on 315 head and neck cancer patients without any radiosensitizing. It has shown a significant decreased rate of dry mouth in the patients receiving cytoprotection [22]. Further studies have indicated a positive impact on other side effects as mucositis, loss of taste and dysphagia [23,24]. The aim of this literature based review is to explore the cytoprotective potential of amifostine in re-irradiated patients.

Cytoprotection for Re-Irradiated Patients

Three studies have investigated the combination of re-irradiation and cytoprotection with amifostine. Busch and colleagues were the first describing the combination of amifostine and simultaneous chemoradiotherapy for the subgroup of recurrent head neck cancer patients. In 1997 they administered a 2nd radiotherapy course in single doses of 2 Gy and a total dose of 40 Gy. Concomitant chemotherapy included 350 mg/m² 5-fluorouracil per day in week 1 and 4 of RT. 28 Patients received 500 mg amifostine IV daily 30 minutes before radiotherapy. The majority of patients developed acute mucositis grade 1 or 2 RTOG only. The grade 3 rate was reduced to <9%.

Antibiotics, analgesics and other local therapeutics could be reduced [25].

Büntzel "et al." [26] had treated 14 patients with recurrent or second malignancies by a simultaneous chemoradiotherapy (20 Gy x 1.5 Gy, carboplatin 70 mg/m² on days 1-5 and 16-20, amifostine 500 mg IV prior each carboplatin infusion). 6/14 patients received additional brachytherapy (10-15 Gy) to increase the local dose because of a residual tumor. The local tumor control was 21.4%. No patient developed grade 3 mucositis. Dysphagia °2 was seen in 5/14 patients, dry mouth was common in 12/14 patients. Serious late toxicities were seen in 1 patient which developed a submental fistula.

Micke "et al." [27] investigated the cytoprotective use of amifostine in the re-irradiation of recurrent tumors in the pelvic region. In palliative intention they had irradiated 14 patients with single doses of 1.8 Gy up to a total dose 39.6 Gy. The application of 500 mg amifostine IV before each radiotherapy allowed to perform this 2nd irradiation course without any grade 3/4 acute toxicity. Their unit also observed no serious late toxicity after a follow-up period of 18 month. The re-irradiation had a good palliative effect concerning symptomatic relief [27].

Conclusions

Re-irradiation alone or in combination with chemotherapy is an effective therapeutic option for recurrent head and neck cancer at the cost of acute and late normal tissue toxicities such as mucositis, dry mouth and soft tissue necrosis. Literature to date demonstrates the potential ability of amifostine to reduce the toxicity from re-irradiation in patients with recurrent head and neck cancer as well as a small number of pelvic tumors. Other scavengers of free radicals such as selenium and vitamin C are routinely recommended for patients undergoing radiotherapy. Further research is therefore suggested to confirm the cytoprotective benefits of amifostine alone or in combination with free radical scavengers in this therapeutic setting.

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