Impact of acute radiation induced toxicity of glutamine administration in several hypofractionated irradiation schedules for head and neck carcinoma

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Abstract

Aim
The aim of this study was to investigate the treatment efficacy, acute and late toxicity using a hypofractionated irradiation schedule combined with oral administration of glutamine (GLN) in elderly patients with advanced squamous cell carcinoma of head and neck (SCCHN).

Methods
In a retrospective manner, we studied 31 patients with advanced SCCHN treated with hypofractionated radiotherapy and administration of GLN. The irradiation schedules consisted of three hypofractionated schedules. The first schedule consisted of 21 irradiation fractions (56.7 Gy) within 29 days by using intensive modulated radiation therapy technique or 3D conformal radiotherapy. The second and the third schedules were performed with 3D conformal techniques by 49.5 Gy in 18 daily fractions and 59.8 Gy in 26 daily fractions. All patients received 30 g powdered GLN daily as soon as oral mucositis was formed with 3D conformal radiotherapy. The second irradiation schedule combined with GLN administration.

Introduction
Several techniques have tried to improve the effectiveness of radiotherapy in advanced squamous cell carcinoma of the head and neck (SCCHN) in patients unsuitable for radical treatment with surgery or chemoradiotherapy (CRT)\(^1\)-\(^3\). However, these patients still need some kind of treatment to control their locoregional disease and to resolve their intense symptoms\(^4\). The hypofractionated accelerated radiotherapy (high dose per fraction) could lead to quick and effective palliation and limit treatment-related toxicity. Significant improvements in toxicity can be achieved by using three-dimensional conformal radiotherapy (3 DCRT) or intensity modulated radiotherapy (IMRT). Moreover, effective use of these therapies is limited by mucositis, xerostomia and other toxicities. Hence, several studies have evaluated the role of glutamine (GLN) for the prevention and treatment of chemo/radiotherapy-induced mucositis\(^5\)-\(^8\).

The aim of our study was to investigate the treatment efficacy, acute and late toxicity using a hypofractionated irradiation schedule combined with oral administration of GLN.

Materials and methods
Data from 31 patients with advanced stage (III/IV) SCCHN cancer treated with hypofractionated RT were retrospectively analysed. Patients were eligible for the study if they were elderly; unsuitable for daily radiation treatment of six weeks; if they had no mouth sores, diabetes and trismus; and if their Karnofsky’s performance status was >60. In addition, patients should have been unsuitable for chemotherapy because of psychiatric disorders, being under medication or because of heart or liver failure. Patient characteristics are shown in Table1. Before treatment initiation, all patients signed an informed consent form concerning the side effects of irradiation.
Radiotherapy treatment

The head position in the treatment planning CT was supine, while the inclination depended upon tumour location. Thickness of the obtained slices was 3 mm from the level above the head through the shoulders. Immobilization with thermoplastic mask was also used. Twenty patients were referred for 3 DCRT either to the ATTIKO University Hospital in Athens or to the Larissa University Hospital in Thessalia. Eleven patients were referred for IMRT to the IASO Hospital in Athens. Radiotherapy was given using a 6 MV or 18 MV linear accelerator with multi-leaf collimator or individualized block after CT simulation and treatment planning using either ECLIPSE (Varian, Palo Alto, CA, USA) or PLATO (Nucletron, The Netherlands) system, depending on the institution. Eleven patients were referred for IMRT by Oncentra Masterplan (4.1; Nucletron). The radiation fields encompassed the gross disease (primary tumour and nodal disease) with a 1 cm margin. Prophylactic nodal irradiation was not undertaken. The plan was to limit the volume of normal tissue to prevent excessive morbidity. The irradiation schedules consisted of three hypofractionated schedules. The first schedule consisted of 21 irradiation fractions (56.7 Gy) without a split, if feasible, within 29 days, by using IMRT techniques. In the 3 DCRT technique, large daily fractions of 2.7 Gy were used for 14 fractions before changing fields to shield the spinal cord. Electrons, usually 9–10 MeV, were used to treat the posterior triangle for the competition of the dose. The second schedule consisted of 18 fractions of 2.75 Gy. The third schedule consisted of 26 fractions with 2.3 Gy. The second and the third

RT schedule

26 × 2.30 Gy 11
21 × 2.70 Gy 11
18 × 2.75 Gy 9

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Table 1 Patient characteristics

<table>
<thead>
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<th>RT schedule</th>
<th>Male/female</th>
<th>77 years (65–87)</th>
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<td>26 × 2.30 Gy</td>
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<td>21 × 2.70 Gy</td>
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Table 1 Patient characteristics

Medial age (range) 77 years (65–87)

Male/female 26/5

Primary

Parotid Stage III/IV 8/1
Tongue Stage III/IV 4/1
Oral cavity Stage III/IV 1/1
Tonsil Stage III/IV 3/0
Lips Stage III/IV 2/0
Ear Stage III/IV 2/0

RT schedule

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scheme) and $T_{new} = 29, 24$ or $36$ days, respectively (accelerated schemes). Thus, NTD represents the dose given in $2$ Gy fractions that would give equivalent biological effect to the new hypofractionated dose, with a value of $NTD_{tumor} = 65.28, 59.5$ or $64.2$ Gy, respectively, depending on the hypofractionated schedule.

In case of calculations for late effect on normal tissues (OAR):

$$NTD_{OAR} = D_{OAR}^{new} \frac{d_{OAR}^{new} + \alpha/\beta}{2 + \alpha/\beta}$$

where $D_{OAR}^{new}$ and $d_{OAR}^{new}$ are total dose and dose per fraction, respectively, for the suggested hypofractionation schedule related to OARs, while the $\alpha/\beta$ for late effects regarding OARS was set to $\alpha/\beta = 3 \times 10^{-12}$. Under the above conditions, $NTD_{OAR} = 64.6, 56.9$ or $63.4$ Gy, respectively, depending on the hypofractionated schedule.

To evaluate the dose constraints for normal tissues, we used the QUANTEC trial corrected for hypofractionation.

Glutamine administration

In all patients, the first dose of GLN commenced at presentation of dysphagia and/or oral mucositis during radiotherapy and completed after three months from the end of irradiation. The daily dose of GLN was $30$ g. Majority of patients ($22$ of $31$; $71\%$) started ingestion of GLN solution at the second week of treatment, while the rest ($9$ of $31$; $29\%$) started ingestion of GLN solution at the beginning of the third week of radiotherapy.

Follow-up

Patients were examined by a radiation oncologist once a week. The severity of skin toxicity and oral mucositis was graded according to the RTOG/EORTC criteria. At each review, patients were specifically asked to evaluate their pain status related to dysphagia on a scale from $0$ (no pain) to $5$ (severe pain). Once dysphagia or mucositis was established, GLN was administered. During irradiation, the maximum pain score and radiation-induced mucosal acute toxicity was taken as the reference value. A comparison was made with the relevant score at the completion of irradiation. In addition, acute skin toxicity as well as late mucosal and skin toxicity were measured. Late toxicity was related to radiation-induced morbidity six months post-irradiation. The patients were followed up after the completion of radiotherapy every three months for the first year and every six months afterwards. The partial response (PR) and complete response (CR), together with any stable or progressive disease, were evaluated.

Follow-up concerning patients with stable disease or response to treatment (partial or complete) was assessed as relapse-free survival (RFS). At each visit, medical history and clinical examination were performed, including flexible nasendoscopy when indicated.

The median follow-up was $18$ months (range: $9–24$).

Medication was prescribed when the patient became symptomatic. The guidelines for pain control of mucositis adhered to World Health Organization (WHO) guidelines (non-narcotics, weak narcotics and narcotics).

Statistical method

The difference in the incidence of acute oral mucositis and dysphagia-related pain before and after GLN administration was evaluated by the chi-square test. Any difference in mean scores of acute oral mucositis and dysphagia-related pain was assessed with the Wilcoxon non-parametric test. The significance level was set at $0.05$. Survival analysis in terms of RFS was performed with the Kaplan–Meier method. The whole analysis was performed with SPSSv10 (Chicago, IL, USA).

Results

Overall CR was seen in $12$ patients ($38.7\%$); $5$ patients ($16.1\%$) exhibited PR, $7$ patients ($22.6\%$) had stable disease and $7$ patients ($22.6\%$) had progressive disease at first follow-up. The Kaplan–Meier curve is shown in Figure 1. The median RFS was...

Acute toxicity
None of the patients developed grade IV skin toxicity; however, 3 patients (9.7%) experienced grade III skin toxicity, 21 patients (67.7%) experienced grade II toxicity and 7 patients (22.6%) experienced grade I skin toxicity.

The maximum dysphagia-related pain score along with acute oral mucositis before and after (last week of irradiation) GLN administration is shown in Table 2. A significant difference was noted in the incidence of both scores after GLN administration ($P < 0.01$, chi-square test). Moreover, as shown in Figure 2, the mean score of dysphagia-related pain and oral mucositis regressed significantly ($P < 0.01$, Wilcoxon test) at the last week of irradiation after GLN administration. There were no treatment-related deaths.

Late toxicity
Late toxicity was monitored for all patients during follow-up. Up to the last follow-up, 8 patients (25%) experienced grade I late radiation skin toxicity. Grade I mucosal toxicity was observed in 10 patients (32%) and grade I xerostomia was noted in 19 cases (61%).

Discussion
Altered fractionation, according to a meta-analysis of radiotherapy in head and neck carcinoma by Bourhis et al., improved survival by 3.4% at 5 years, although accelerated schedules with dose reduction improved survival in significantly by only 1.7%16. Most of these patients died of locoregional disease progression14–17,20. The addition of chemotherapy improved disease control and long-term survival in patients fit to receive the CRT regimen16,17. Further, these patients needed palliative treatment to control their locoregional disease and alleviate their disturbing symptoms.

However, in the current literature, not much data exists on optimal palliative RT treatment regarding the daily dose and fractionation schedule for incurable SCCHN cancer. A short radiotherapy regimen seems more appropriate from a radiobiological point of view20,21. The treatment is completed before starting repopulation. In addition, considering the fact that patients in this group are elderly with significant comorbidities, it is almost compulsory to keep the overall treatment time as short as possible20,21. In any case, the main aspect that should be taken into account is definitely the expected toxicity with the implementation of hypofractionated schedules.

The present study reports three hypofractionated accelerated radiotherapy regimens for palliation of locoregionally advanced and incurable SCCHN cancer without chemotherapy but with concomitant use of GLN for reduction of mucositis.

Glutamine is a conditionally essential amino acid that has multiple benefits by providing energy for immune cells, supporting stem cell division, protecting the gut lining, and providing building blocks for glutathione, a crucial antioxidant. In the context of cancer, glutamine has been shown to improve immune function, reduce oxidative stress, and potentially slow tumor growth. Glutamine supplementation has been studied in various clinical settings, including radiotherapy, chemotherapy, and surgical stress, with promising results in terms of reducing toxicity and improving outcomes. Future research is needed to further elucidate the optimal use of glutamine in cancer management.
well-defined functions in human biological processes as described by Sonis\textsuperscript{23}. Intracellular GLN, via glutathione, neutralizes the reactive radicals derived from radiation and/or chemotherapy, preventing further DNA damage\textsuperscript{24–26}. Another mechanism during RT is realizing up-regulation and message generation, where intracellular signalling molecules such as NF-κB induce expression of genes involved in inflammation. Intracellular glutamine decreases NF-κB expression\textsuperscript{27}. During signalling and amplification, a variety of pro-inflammatory cytokines are produced that cause extended tissue injury. GLN down-regulates these cytokines, particularly TNF-α, thus closing the inflammatory feedback loop. In addition, intracellular glutamine reduces apoptosis of epithelial cells throughout these initial phases\textsuperscript{28–32}, as it is a primary oxidative fuel of the gut epithelium and is necessary for the maintenance of integrity of the gut structure during normal and stress conditions\textsuperscript{5–8}. Moreover, a significant amount of GLN is provided through skeletal muscles during hypercatabolic states such as cancer\textsuperscript{33}. Hence, glutamine depletion under some circumstances compromises the acid–base balance, immune functions, epithelial integrity and facilitates bacterial translocation in the gut. However, due to its protective functions against oxidative injury in normal tissue, depletion of GLN may increase the extent of cancerous tissue damage caused by radiotherapy. In conclusion, glutamine supplementation normalizes the levels in the body, which explains its selective radioprotective actions on normal tissues\textsuperscript{5–8,33}.

Fukui et al.\textsuperscript{34} studied the prevention of oral mucositis with the use of GLN in 15 patients with oesophageal cancer who received chemotherapy. Seven courses of GLN were administered in six patients with grade I oral mucositis. After seven courses of GLN, in these six patients, oral mucositis declined from grade I to 0. This result indicates that GLN has preventive or reducing effects on oral mucositis.

None of the patients in our study developed grade IV acute skin toxicity, while only three patients had grade III mucositis which regressed after GLN administration. Relative low mucositis toxicity in the present study may be related to GLN administration. Mucosal toxicity was confirmed in these three patients receiving low dose of GLN due to non-conformity to the administration schedule; these patients did not receive the full daily dose of 30 g. Although retrospective, the present study is the first to evaluate the role of GLN in the reduction of the side effects of chemotherapy. Our results showed a significant reduction in mucositis and pain in radiotherapy regimen. In addition, we demonstrated that 3 DCRT and IMRT techniques allow the hypofractionation schedules with concomitant GLN administration. The acute and late toxicity rates were acceptable. It was observed that maximum dysphagia related to the mucositis regressed significantly with GLN addition. Symptoms relief together with acute and late treatment-related toxicity are the important components in the equation, evaluating whether or not a treatment provides good palliation to patients.

In the present study, we chose hypofractionated accelerated schedule of RT, which in theory provides better targeting of tumours with relatively low α/β ratios, such as hypoxic tumours and tumours with high repopulation ability\textsuperscript{10–12}. Despite the benefits of palliative hypofractionated accelerated radiotherapy in patients with advanced solid tumours, there is a dearth of such data in advanced SCCHN cancer\textsuperscript{35–41}. There are inadequate information on time, dose and fractionation. Practices have ranged from using a short course of large daily fractions for achieving palliation to delivering conventionally fractionated radical doses of 60–70 Gy in the hope of prolonging the duration of palliation\textsuperscript{19,35–41}, there is a long discussion on whether or not prolonged radiotherapy, identical to curative schedules with high toxicity, is necessary. Several studies focused on hypofractionated accelerated palliative radiotherapy for advanced SCCHN cancer without GLN administration\textsuperscript{36–41}. Toxicity and local response or disease progression have been already studied; however, toxicity remains the only contradiction in using a hypofractionated schedule.

In a study conducted on 505 patients with stage IV SCCHN by Mohanti et al.\textsuperscript{37}, the radiotherapy schedule comprised 20 Gy in five fractions, once daily over a week. Good symptom relief was reported in more than 50% of the patients. One month post-irradiation, 189 patients (37%) achieved PR, and eventually, they had good physical state. Median overall survival with palliative radiotherapy was 200 days. In this study, the biological effective dose for tumour was 44.9 Gy, while it 28 Gy for the normal tissue; this was too small to cause severe toxicity.

Further, Porceddu et al.\textsuperscript{38} observed 35 patients treated with a hypofractionated radiotherapy schedule that comprised 30 Gy in five fractions, two fractions per week, at least three days a week, with an additional boost of 6 Gy for limited volume disease. The overall objective response rate was 80%. The median time to progression and death was 3.9 and 6.1 months, respectively, with seven (20%) patients surviving beyond a year. Overall quality of life improved and symptom control were reported in 13 (63%) and 14 (67%) of the 21 assessable patients. Grade III mucositis and dysphagia were seen in 26% and 11% patients, respectively. The biological equivalent dose for the normal tissue in this study is 64.8 Gy, which was high enough to cause mucositis unlike the expected efficacy. In a retrospective review by Erkal et al.\textsuperscript{39}, 40 patients with advanced...
neck disease were treated with either 30 Gy in 10 fractions at five per week or 20 Gy at 10 Gy per fraction with a one-week inter-fraction interval. There was a good one-year response rate of 77% and 48%, respectively, with a similar symptomatic response rate of 68% and 38%, respectively. While no patients suffered from severe late complications, the acute toxicity could not be ascertained from this retrospective study.

In 110 patients, Agarwal et al. applied a hypofractionated schedule of 40 Gy in 16 fractions in 3 ½ weeks, each fraction comprising 2.5 Gy daily. Patients with complete or partial disease regression after initially planned 40 Gy were offered further dose escalation (up to 10 Gy in 4 fractions for a maximum dose of 50 Gy in 20 fractions). Eleven patients (10%) had CR and 80 (73%) patients had CR and PR. The biological equivalent dose for the tumour was 58.35 Gy, similar to that in our schedule, and the response was very good in terms of pain relief. The overall RFS at 12 months was 58.35% in terms of pain relief. According to our study, it seems that GLN administration was the factor that helped in acute and late toxicity.

Koukourakis et al. studied 43 patients with local advanced head and neck cancer. Conformal hypofractionated/accelerated RT with amifostine cytoprotection (2.7 Gy/Fraction, 21 fractions in 4 weeks) was combined with chemotherapy. Grade III to IV mucositis occurred in 7 of 43 (16.2%) patients and fungal infections occurred in 18 of 43 (41.8%) patients. Radiation dermatitis was not aggravated. A severe late radiation sequel consisted of laryngeal oedema (9% laryngeal cases) and cervical strictures (33% hypopharyngeal cases). Good salivary function was preserved in 6 of 11 (54.5%) nasopharyngeal cancer patients. CR rate was 68.5%, reaching 77.2% in patients with minor radiotherapy delays. The 24-month local control and survival rates were 72.3% and 91%, respectively (median follow-up was 13 months).

All previous studies showed a toxicity range of grade II/III oral mucositis, between 16% and 65%, in various hypofractionated schedules but without GLN administration. Our study demonstrates that in elderly patients, with comorbidities and unsuitable for daily irradiation and chemotherapy, an alternative schedule of hypofractionation is possible when combined with GLN administration by keeping the grade II oral acute toxicity down to 10%, while grade III toxicity was eliminated. In this setting, symptom relief and toxicity were improved with GLN administration. Due to the retrospective nature of the present study, it seems that the addition of oral GLN in a palliative hypofractionated regimen of radiotherapy considerably contributes to the regression of radiation-induced toxicity. Quality of life remains the most vital issue of all. However, to extract safe results, the potential impact of GLN administration on radiation-induced toxicity should be accurately assessed in a prospective study of patients receiving palliative radiotherapy.

References