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Original article

The effects of oral glutamine on clinical and survival outcomes of non-small cell lung cancer patients treated with chemoradiotherapy☆

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SUMMARY

Purpose: To assess the efficacy of oral glutamine (Gln) supplementation on clinical and survival outcomes of patients with locally advanced non-small cell lung cancer (LA-NSCLC).

Materials/methods: Between 2010 and 2014, 122 stage III NSCLC patients were retrospectively analyzed. All patients received curative intent chemoradiotherapy (CRT). Prophylactic oral Gln powder was applied at a dose of 10 g tid. Effect of oral Gln supplementation in the prevention of severe (≥grade 2–3) acute radiation-induced esophagitis (ARE) and weight loss, and their relation with overall survival (OS) and disease-free survival (DFS) was measured.

Results: Median follow-up was 13.14 months (range; 1.97–55.36). Fifty-six (46%) patients had received oral Gln. Severe ARE was significantly lower in Gln-supplemented group (30% vs 70%; $p = 0.002$). Gln-free patients demonstrated a higher weight loss ($p = 0.0001$). In multivariate analysis hemoglobin (hb) level (<12 g/dL; $p = 0.01$) and nodal stage (N3; $p = 0.01$) were poor prognostic factors that affect OS; Weight loss ($p = 0.06$) and Gln-free ($p = 0.05$) reached nearly significant levels that poorly affect OS. Similarly, nodal stage (N3, $p = 0.014$) and Gln-free ($p = 0.035$) were poor prognostic factors that affect DFS. Weight loss (≥2%, $p = 0.06$) and hb level (<12 g/dL, $p = 0.07$) reached borderline significance that poorly affect DFS. Nodal stage (N3) was the only poor prognostic factor that affect OS and DFS in univariate analysis ($p = 0.01$, $p = 0.009$; respectively).

Conclusion: Oral Gln supplementation significantly reduces grade 2–3 esophagitis and weight loss and also no negative impact on tumor control and survival outcomes in patients with LA-NSCLC.

1. Introduction

Acute radiation-induced esophagitis (ARE) is the most common side-effect of thoracic radiotherapy (RT) in patients with locally advanced non-small cell lung cancer. To use more influential regimens has resulted in enhanced incidence and severity of this toxicity [1–5]. Approximately 5–100% of patients are influenced by this toxicity [6]. ARE may affect not only the planned treatment but also the quality of life of patients that may result in a decrease in tumor control and survival rates. Modifications and dose reductions in the treatment schedule can directly influence patient survival. So, in order to reduce this toxicity, advanced RT techniques and radioprotective agents were tested. Three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy [7] can be used to diminish irradiated esophageal volumes and doses but toxicity couldn't be effectively prevented due to the proximity of the esophagus to the treatment volumes.

Recently, Glutamine (Gln) has been most popular agent because of its radioprotective properties. The amino acid Gln is frequently used by rapidly dividing cells as the main energy fuel and/or nitrogen source for optimal functioning [8]. In hypermetabolic situations, for example in cancer patients, plasma levels of Gln are inadequate to compensate for the increased demand and Gln deficiency eventually develops. In addition, intensive treatment modalities such as RT and chemotherapy are related with low plasma levels of Gln [9]. When the host is under the impression of stressors that increase its metabolic demands, Gln is withdrawn from the skeletal muscle and released into cycle, which may essentially contribute to host cachexia [10,11].

The first experimental animal studies demonstrated that, in a critical state, Gln support may be useful because of the

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improvement of immunity. Later, many human studies showed that Gln support results in beneficial effects on nutrition indicators, nitrogen metabolism and immunologic parameters [12–15].

The characteristics of cancer cells are metabolic independence and five to ten times faster rate of Gln consumption than nonmalignant cells [11]. Therefore, there is increasing concern that Gln might activate tumor progression and hence adversely affect outcomes. Several cell line and animal studies showed that Gln supplementation caused tumor progression in the host [11,16] but when the studies planned in animals and in phase-1 clinical trials, the results were found to be disappointing and the studies were unsustainable because of side effects. As a consequence of these uncertain results, the only way to disclose the effect of Gln on tumor progression and outcomes of cancer treatment is on the basis of in vivo studies. Therefore, we aimed to assess the efficacy of oral Gln supplementation in the prevention of ARE and its complications in NSCLC patients treated for curative intent and to determine the predictive role of clinical parameters on survival.

2. Materials and methods

2.1. Patient population

Between 2010 and 2014, 122 patients with locally advanced NSCLC were included. A retrospective study of the database was obtained from our department. Patients were inoperable on the basis of mediastinal lymph node involvement (N2 or N3), or bulky disease (T3 or T4). Inclusion criteria for our study: newly diagnosed, biopsy-proven NSCLC staged as IIIB (and medically inoperable IIIA); treatment with concurrent chemotherapy and definitive 3D-CRT; age $\geq$18, Karnofsky Performance Status (KPS) $\geq$ 70; the availability of esophageal dose-volume histograms (DVHs); the availability of patients records from weekly 3D-CRT treatments and hospital computerized data; mean esophageal dose $\leq$34 Gy and/or percent of esophagus volume receiving 60 (V60)< 30%, no pretreatment dysphagia or ingestion difficulties; no prior history of thoracic RT or chemotherapy; body mass index (BMI) $\geq$ 18 kg/m^2; no known Gln allergy; and not receiving another dietary supplement during the treatment.

The study was confirmed by the board of our university before the start of the study and conducted according to the ethical principles of the latest version of the Helsinki Declaration.

2.2. Treatment

All patients underwent 3D-CRT. Planning CT slides were obtained (3 mm thick) from the level of the mandible to the lower edge of the liver. The required CT images were sent directly to the 3D planning system (Eclipse version 8.2, Varian, USA).

All patients had their targets identified in accordance with the International Commission on Radiation Units and Measurements Report (ICRU 50). Gross tumor volume (GTV) involved all detectable tumors and any abnormally enlarged hilar and/or mediastinal lymph nodes $\geq$1 cm observed on CT scans. Clinical target volume (CTV) was identified by adding 0.5–1 cm margin to GTV. Planning target volume (PTV) was identified by adding 1–1.5 cm margin to CTV. Contouring of target volumes and critical organs was fulfilled on each CT slide. All patients received RT using three-dimensional conformal technique with 1.8–2 Gy fraction doses, 5 days a week, for a total dose of 61.2–64 Gy. Concurrent chemotherapy was prescribed as “weekly Cisplatin or carboplatin and pactitaxel” or “cisplatin and etoposide”, or “cisplatin and vinorelbine”, every 21 day in accordance with our clinical protocols.

2.3. Glutamine supplementation

Prophylactic Gln powder is one of the major dietary supplements that are frequently recommended to our NSCLC patients. According to our patient' s records, fifty-six (46%) patients received oral Gln powder at a dose of 30 g/day (10 g/8 h orally, dissolved in water or fruit juices) starting 1 week before RT and continuing for 2 weeks after completion of RT. Sixty-six patients (54%) didn't receive oral Gln powder due to their choice or economic reasons.

2.4. Patient evaluation and scoring of esophagitis

All available chart records were utilized and patient's data were examined for determining the ARE incidence, grade of toxicity using Radiation Oncology Group/European Organization for Research and Treatment of Cancer criteria [17] (Table 1), weight changes (absolute difference between pre- and post-treatment weight measures) and percentage of weight changes.

Cases exhibiting a pretreatment hb level lower than 12 g/dL were considered as anemia.

2.5. Clinical evaluation and follow-up

As an institutional policy, the first response evaluation is performed 8 weeks from the completion of treatment using Computed tomography (CT) or Fluorodeoxyglucose (FDG)-Positron emission tomography FDG-PET–CT scan. In cases where response to the treatment is assessed by CT scan, The Response Evaluation Criteria in Solid Tumors (RECIST)-2009 guidelines are used [18]; but in cases where response to the treatment is assessed by FDG-PET–CT scan the European Organization for Research and Treatment of Cancer (EORTC)-1999 guidelines are used [19].

2.6. The end points

The first primary end points of this study were to assess the weight loss, percentage of weight loss and ARE incidence/severity. The second primary end points of this study were to evaluate disease-free survival (DFS) and overall survival (OS). DFS was defined as the time from the date of completion of RT to the date of the documented recurrence. OS was defined as the date of completion of RT to the date of death or last follow-up.

Table 1
Radiation Therapy Oncology Group (RTOG) acute radiation-induced esophageal morbidity scoring criteria.

Grade	Description
0	No change
1	Mild dysphagia or odynophagia, requiring topical anesthetic, non-narcotic agents, or soft diet
2	Moderate dysphagia or odynophagia, requiring narcotic agents or liquid diet
3	Severe dysphagia or odynophagia with dehydration or weight loss (>15% of pretreatment baseline) requiring nasogastric feeding
4	Complete stricture, ulceration, perforation or fistula
5	Death

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