The Effect of the Wound Healing Properties of Glutamine on Skin Toxicities and Esophagitis in Breast Cancer Radiotherapy

Meme Kanseri Radyoterapisinde Glutaminin Yara İyileştirme Özelliklerinin Cilt Toksisiteleri ve Özofajit Üzerine Etkisi

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ABSTRACT

Objective: Acute toxicities of breast cancer radiotherapy are weakness, skin reactions and esophagitis. Glutamine is an essential amino acid that forms the basic energy source of the immune system cells andthe intestine inner surface cells and plays an essential role in the delivery of acid-base balance and the nerve transmission. In our study, we aimed to evaluate the effect of the wound healing properties of glutamine on skin toxicities and esophagitis.

Materials and Methods: Fifty six patients were included in the study. The results of 28 patients who used 30 g(10g/8h) Glutamine during radiotherapy and 28 patients without glutamine usage were evaluated. 40-60 GyRT was given with a single fraction of 2-2.66 Gy per dayin five fractions weekly. Skin reactions and esophagitis status of the patients were evaluated weekly. Toxicities were recorded according to Radiation Toxicity Evaluation Criteria (RTOG).

Results: The mean age was 53 years (29-86). 42 patientshad underwent breast-conserving surgery and 14 patients had underwent modified radical mastectomy. 39 patients had stage 2, 17 had stage 3 dissease. Dysphagia had developed in 23 patients (42.6%). Grade 1 dysphagia was detected in 20 patients and grade 2 dysphagia was detected in 3 patients. Skin reaction had developed in 38 patients (70.4%). 17 of these had grade 1, 20 had grade 2 and 1 had grade 3 skin reaction.Dysphagia (P <0.001) and skin reaction (P = 0.014) were statistically significant lower in the group receiving glutamine. In premenopausal patients, significantly more dysphagia (p: 0.003) and skin reactions (p: 0.018) were observed than postmenopausal patients. Skin reaction and dysphagia were observed less in the group that received hypofractioned RT. Dysphagia was observed more in the MRM receiving group according to the surgery type.
It was observed that there was no effect of stage, age, T-N stage, tumor side, pathological type on skin reaction and dysphagia.

Conclusion: The use of glutamine to reduce side effects during breast cancer radiotherapy is not a standard procedure. However, the use of glutamine in the treatment of dysphagia and skin reactions during breast radiotherapy may be useful in reducing the severity of the toxicities by it's wound healing effect.

Key Words: Breast cancer, radiotherapy, glutamine

Received: 09.29.2019 **Accepted:** 01.31.2020

ÖZET

Amaç: Meme kanseri radyoterapisinin akut toksisiteleri zayıflık, cilt reaksiyonları ve özofajittir. Glutamin, bağışıklık sistemi hücrelerinin ve bağırsak iç yüzey hücrelerinin temel enerji kaynağını oluşturan ve asit-baz dengesinin ve sinir iletiminin sağlanmasında önemli bir rol oynayan esansiyel bir amino asittir.
Çalışmamızda glutamin yara iyileşme özelliklerinin cilt toksisiteleri ve özofajit üzerindeki etkisini değerlendirmeyi amaçladık.

Yöntem: Çalışmaya 56 hasta dahil edildi. Radyoterapi sırasında 30 g (10 g / 8 saat) Glutamin kullanan 28 hastanın ve glutamin kullanmayan 28 hastanın sonuçları değerlendirildi. Haftada beş fraksiyonda günde 2-2.66 Gy'lik tek bir fraksiyon ile 40-60 GyRT verildi. Hastaların cilt reaksiyonları ve özofajit durumu haftalık olarak değerlendirildi. Toksisiteler Radyasyon Toksisitesi Değerlendirme Kriterlerine (RTOG) göre kaydedildi.

Bulgular: Yaş ortalaması 53 (29-86) idi. 42 hastaya meme koruyucu cerrahi ve 14 hastaya modifiye radikal mastektomi uygulandı. 39 hastada evre 2, 17 hastada evre 3 hastalık mevcuttu. 23 hastada (% 42.6) disfaji gelişti. 20 hastada grad 1 disfaji, 3 hastada grad 2 disfaji saptandı. 38 hastada (% 70.4) cilt reaksiyonu gelişti. Bunlardan 17'sinde grad 1, 20'sinde grad 2 ve 1'inde grad 3 deri reaksiyonu vardı. Disfaji (P <0.001) ve cilt reaksiyonu (P = 0.014) glutamin alan grupta istatistiksel olarak anlamlı derecede düşüktü. Premenopozal hastalarda postmenopozal hastalara göre anlamlı derecede daha fazla disfaji (p: 0.003) ve cilt reaksiyonları (p: 0.018) gözlenmiştir. Hipofraksiyonlu RT alan grupta deri reaksiyonu ve disfaji daha az gözlendi. Disfaji, cerrahi tipine göre MRM uygulanan grupta daha fazla gözlendi.
Evre, yaş, T-N evresi, tümör tarafı, patolojik tipin cilt reaksiyonu ve disfaji üzerine etkisi olmadığı gözlendi.

Sonuç: Meme kanseri radyoterapisi sırasında yan etkileri azaltmak için glutamin kullanımı standart bir prosedür değildir. Bununla birlikte, meme radyoterapisi sırasında disfaji ve cilt reaksiyonlarının tedavisinde glutamin kullanımı, yara iyileştirici etkisi ile toksisitelerin şiddetini azaltmada yararlı olabilir.

Anahtar Sözcükler: Meme kanseri, radyoterapi, glutamin

Geliş Tarihi: 29.9.2019 **Kabul Tarihi:** 31.01.2020

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doi:http://dx.doi.org/10.12996/gmj.2020.44

INTRODUCTION

Breast cancer is the most common type of cancer in women and ranks 5th in cancer-related deaths according to the world health organization data(1). Different treatment modalities are applied in the treatment of breast cancer according to the stage of the disease. The general approach is surgery followed by adjuvant chemotherapy ± radiotherapy. Patients with locally advanced disease are treated with neoadjuvant therapy.

Radiation therapy plays an important role in increasing the local control in the treatment of breast cancer. (2) Especiallyin cases with lymph node involvement, esophagus and skin that remains in the treatment area were affected by radiation exposure. Data on esophageal toxicity, which is more rare in breast cancer patients, were generally obtained with the results of patients who underwent thoracic radiotherapy. Radiation-induced acute esophagitis is one of the most common toxicities of supraclavicular region irradiation.

Acute oesophagitis-related symptoms are associated with early esophageal mucositis and usually occur as dysphagia, odynophagia and substrenal pain after two or three weeks of the treatment (3). Radiotherapy technique and the dose of esophagus are important factors in esophageal toxicity. Dose-volume-toxicity limits were illustrated more detailed by the study of Emami et al, QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) and RTOG (Radiation Therapy Oncology Group) (4). Radiotherapy scheme, concurrent chemotherapy and reflux are also the effective factors for esophagitis (5,6,7,8).

Glutamine (GLN) is a radioprotective agent with a neutral amino acid structure. It is abundant in the liver, kidney, skeletal muscles and brain in human body. Particularly in hypermetabolic conditions, it can be used as a nitrogen source and / or an alternative energy supply by rapidly dividing cells such as blood elements. Under normal conditions, glutamine production may meet the needs of the body but in pathological conditions and especially in catabolic processes, it may be inadequate to meet the demands of organs such as intestines, kidneys, liver and immune system which require glutamine for their normal functions. Glutamine deficiency can result in severe complications including multiple organ failure (9,10).

In this study, we aimed to reduce the acute oesophagitis and skin reactions due to RT by providing oral glutamine supplementation and thus to improve treatment compliance and patient quality of life.

MATERIALS ad METHODS

Fifty six breast cancer patients who underwent RT with a supraclavicular radiotherapy area in our clinic between 2017-2018 were included in this study. The criterias for patient selections were: they did not receive RT before, did not receive any treatment due to pre-treatment dysphagia or digestive disorders and did not use additional nutritional products during the treatment. The results of the patients were evaluated retrospectively.

Glutamine was given 30g(10g/8hr orally, with water or juice) daily for during RT to two weeks after RT. Glutamine was well tolerated by all patients. This dose was the reported dose in the literature that it reduced the incidence of acute radiation-induced esophagitis, weight loss (11) and grad 2 ve4 mucositis (12). Intensity Modulated Radiation Therapy (IMRT) planning was performed to all of the patients.

Target volumes and organs at risk (esophagus, spinal cord, lungs, heart, opposite breast, brachial plexus) were contoured based on RTOG contouring atlas data. The esophagus was contoured from the cricoid cartilage to the gastroesophageal junction. All glandular breast tissue and chest wall were located within the CTV volume (superiorly second intercostal space that combined with supraclavicular field, inferior the end of the breast tissue, medial and lateral / posterior boundary will be determined by considering at tm placement, generally not to exceed the mid axillary line in the lateral and include the costa-sternal junction line in the medial) (13).

The supraclavicular field was covered by the first-second intercostal space at the inferior, to the thyrocricoid space in the superior, medial border of the sternocleidomastoid muscle to 1 cm lateral of the midline at the medial and the vertical line passing through the anterior axillary fold at the lateral. PTV was created with a 0.3-0.5 cm margin to the CTV. 40-64Gy RT was administered with a dose of 2-2.66Gy single fraction per day, five fractions weekly.

Acute radiation-induced esophagitis and skin toxicity were assessed and recorded weekly by radiation oncology specialists according to the RTOG-ARIE scoring criteria (Table 1, 2). The patients weekly follow-up had continued for one month after radiotherapy. Age, hypofraction or conventional RT doses, tumor pathology, location, T and N stage, esophagus doses which may be related with acute esophagitis and dermatitis were evaluated. SPSS version 17 was used for statistical analysis. P <0.05 was considered as statistically significant.

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

Stage	Definition
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

Table 2.RTOG (Radiation Therapy Oncology Group) radiation induced acute skin toxicity score

Stage	Definition
0	No change over baseline
1	Follicular, faint or dull erythema/ epilation/ dry desquamation/ decreased sweating
2	Tender or bright erythema, patchy moist desquamation/ moderate edema
3	Confluent, moist desquamation other then skin folds, pitting edema
4	Ulceration, hemorrhage, necrosis

RESULTS

The mean age of the patients was 52.5 years (29 - 86). In thirty-four cases, tumor were located at the left side and 22 at the right side. Pre and post menopausal cases were 28 in both groups. 42 (75%) patients hadundergone breast conserving surgery while 14 (25%) hadreceived modified radical mastectomy. 46 (82.1%) cases had invasive ductal, 4 (7.1%) had invasive lobular, 3 (5.4%) had medullary and the remaining three (5.4%) had mucinous, papillary and tubular carcinoma. Stage 2 disease was observed in 39 (69.6%) cases and 17 (30.4%) patients had stage 3 disease. 19 patients had perineural invasion and 22 had perivascular invasion. Distribution of patients according to lymph node involvement; 45 cases (80.4%) had N1, 9 had N2 (16.1%) and 2 had N3 (3.6%) disease.

While 47 (66.1%) patients received a dose of 46-60 Gy RT with a daily 2 Gy conventional fractionation, the other 17 patients (33.9%) received 40Gy with hypofractional scheme, a daily dose of 2.6 Gy. BED 10 values were calculated of patients which treated with different fractional scheme. The patients were divided into two groups according the BED value as over and under BED 62.5Gy. There was no difference in comparison of these two groups according to dysphagia (p: 0.97), while the skin reaction on BED10 over 62.5 Gy was significantly higher (p: 0.02).

The mean esophagus dose was 313cGy (min: 51.4cGy-max: 4378.7cGy). Dysphagia had developed in 23 patients (42.6%). In 20 (37%) patients grade 1 dysphagia and in 3 (5.6%) patients grade 2 dysphagia were detected. Skin reaction had developed in 38 patients (70.4%). 17 (30.4%) of the cases had grade 1, 20 (35.7%) had grade 2 and 1 (1.8%) had grade 3 skin reactions(Table 3).

Table 3. Patient characteristics

Age		**Median (interval)** 52.5(29-86)
	n	**%**
Menopause status		
Premenopause	28	50
Postmenopause	28	50
Breast side		
Right	22	39.3
Left	34	60.7
Surgery type		
Breast conserving surgery	42	75
Mastectomy	14	25
Tumor pathology		
İnvazive ductal	46	82.1
İnvazive lobular	4	7.1
Medullary	3	5.4
Other(tubular, mucinous, papillary)	3	5.4
Stage		
II	39	69.6
III	17	30.4
Radiotherapy schema		
Conventional	37	66.1
Hypofractionated	19	33.9
Dysphagia 54 cases		
Positive	23	42.6
Negative	31	57.4
Dysphagia grade		
Grade 0	31	57.4
Grade 1	20	37
Grade 2	3	5.6
Skin reaction 54 cases		
Positive	38	70.4
Negative	16	29.6
Skin reaction grade		
Grade 0	16	29.6
Grade 1	17	30.4
Grade 2	20	35.7
Grade 3	1	1.8

DUSCUSSION

The aim of breast cancer radiotherapy is to increase local control in breast tissue and regional lymphatics. It has been shown in the studies that adjuvant radiotherapy has a survival advantage in the long-term follow-up of patients. (14) The aim of the breast radiotherapy is to provide maximum preservation of normal tissues and to give homogenousdose to tumor.

Esophagus is affected especially in the supraclavicular region applicationof breast radiation. The dose of esophagus may be partially reduced by the correct positioning and techniques such as IMRT, but it may not always provide adequate protection. Protective agents such as glutamine may be utilized to protect the esophagus from radiation effects. Glutamine has been used in head and neck cancers (15) and lung cancer patients as an effective protective agent to reduce radiation-related esophagitis (16).

Radiation dermatitis is also an important problem in breast radiotherapy and there is no gold standard in the treatment of radiation-related dermatitis. Different degrees of radiation dermatitis, such as erythema, wet desquamation, ulceration, can be seen during treatment and must be controlled forcompleting the treatment. Glutamine, an anabolic amino acid, has been shown to improve wound healing and improve wound matrix formation in burn patients (17). It was also shown that glutamine support can reduce the nosocomial infections and the pain that needs narcotic agents(10.18).

Peterson et al. demonstrated that the use of glutamine hadsignificantly reduced the severity of oral mucositis compared to the non glutaminegroup in a phase 3 randomized study involving 326 breast cancer patients (19).Algara et al. found that the rate of acute esophagitis had decreased with the use of glutamine in 75 patients who underwent thoracic radiotherapy (11). In the same series Topkan et al. had shown that glutamine is effective in controlling acute and late radiation-induced esophagitis and also contributes to a reduction in the duration of treatment due to esophagitis (20).In our study, we found that radiation induced esophagitis had significantly decreased in patients using glutamine (P <0.001).

Although there have been many studies that researched different parameters for radiation induced esophagitis, such as mean esophagus dose, maximum esophagus point dose, we could not obtain a clear dose-response relation. The maximum dose of esophagus (Dmax> 5117 cGy) and the mean esophagus dose (Dmean> 1487 cGy) were significant predictive values for the development of esophagitis due to radiotherapy and were shown by Etiz et al. (21). Zhang et al. detected that V40 and V50 values were important fordevelopment of acute esophagitis(229.In our study, in which we evaluated the patients using glutamine during radiotherapy for local advanced lung cancer, we found different degrees of dysphagia in almost all patients with a mean esophagus dose of > 20 Gy (10). According to these data, consistent results could not be obtained in studies for relationship between radiation dose and esophagitis. In our study, our mean dose was 313 cGy and the most patients had grade 1 dysphagia.

Radiotherapy is critical inbreast cancer treatment and according to the data of the studies, approximately 90% of the patients treated with radiotherapy had different degrees of skin toxicity (24). The treatment could be interrupted for different levels of radiation dermatities like erythema, wet desquamation and ulceration and there is no gold standard in the treatment of them. It was thought that Glutamine, an anabolic effective amino acid, can be used to control the findings of radiation dermatitis by it's improving wound matrix formation effect, especially in burn patients. Küçüktülü et al. found 89% grade 1 skin toxicity in glutamine group and 80% grade 2 skin toxicity in the placebo group in their randomized trials of 40 patients diagnosed with breast cancer and showed that the use of glutamine decreased the skin toxicity (p <0.001) (17).

Lopez-vaquero et al. found a significant reduction in the severity of skin toxicity in patients using glutamine in head and neck cancer patientsin their randomized double-blind study that had evaluated radiotherapy mucositis and cervico-facial dermatitis (23). In our study, we found that dermatitis secondary to radiotherapy had decreased statistically significantly in patients using glutamine (P = 0.014).

There are limited number of studies showing the relationship between radiation dermatitis and glutamine and our results are consistent with the results of current studies.

According to operation type, dysphagia was more common but skin reaction was similar in MRM and BCS. It was thought that the patient in the MRM group was in more advanced stages and in these patients larger area radiotherapy was applied therefore dysphagia was seen to be more common.

There is no significant difference in early side effects in hypofraction schemas. In our study, hypofractionated group had significantly less dysphagia (p: 0.003) andhad no difference in skin reaction (p: 0.25).

Postmenopausal patients had statistically significant less skin reaction (p: 0.018) and less dysphagia (p: 0.003) than premenopausal patients. Tissue renewal and wound healing was delayed at advanced ages. Glutamine, which plays a major role in the continuity of the sustained dividing and proliferating cells, provides more benefit to this group of patients.Dysphagia (p: 0.01) and skin reaction (p: 0.032) were significantly higher in the perinural invasion group. Dysphagia was less common in patients without perivascular invasion (p: 0.001). Skin reaction was the same in two groups. These data can help in the decision to start glutamine in patients with perineural and perivascular invasion.

In conclusion, the use of oral glutamine improves the quality of life of patients in adjuvant breast radiotherapy with supraclavicular region by reducing the severity and frequency ofradiation-induced acute esophagitis and skin reactions and reduces the unplanned treatment intervals due to side effects. With this data, glutamine may be recommended in breast cancer patients receiving supraclavicular radiotherapy.

Conflict of interest
No conflict of interest was declared by the authors.

Acknowledgments:
Sule Karabulut Gul(design study, practical performance, data analysis, preparation manuscript, critical review manuscript), Huseyin Tepetam(practical performance, statistical analysis), Beyhan Ceylaner Bicakci(practical performance, data analysis), Fatih Demircioglu(practical performance), Gokhan Yaprak(writing).

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clın 2018;68:394-424
2.Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V et.al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005:17;366:2087-106
3.Haydaroglu A.Modern Radiotherapy Applications in Breast Cancer. Ege University Publishing, Izmir, 2014;123-139
4. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal TissueEffects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J RadiatOncolBiolPhys 2010:1;76:3-9
5. Maguire PD, Sibley GS, Zhou SM, Jamieson TA, Light KL, Antoine PA et al. Clinical and dosimetric predictors of radiation-induced esophageal toxicity. Int J RadiatOncolBiolPhys 1999; 45:97
6. Ohe Y. Chemoradiotherapy for lungvcancer: current status and perspectives.Int J ClinOncol2004;9:435-43
7. Werner-Wasik M, Paulus R, Curran WJ Jr, Byhardt R. Acute esophagitis and late lung toxicity in concurrent chemoradiotherapy trials in patientswith locally advanced non-small cell lung cancer: Analysis of the Radiation Therapy Oncology Group (RTOG) database. Clin Lung Cancer 2011;12:245-51
8. Halperin EC, Wazer DE, Perez CA, BradyLW. Perez&Brady's Principles and Practice of Radiation Oncology. 6th ed. Philadelphia: LippincottWilliams&Wilkins; 2013: 938-73
9. Häberle J, Görg B, Rutsch F, Schmidt E, Toutain A, Benoist JF, et al. Congenital glutamine deficiency with glutamine synthetase mutations. N Engl J Med 2005;353:1926-33
10. Gul SK,Oruç AF, Atalay R, Yavuz BB, Gedik D, Aksu A. The Effect of Oral Glutamine in the Prevention of Radiotherapy Related Esophagitis and Weight Loss in Lung Cancer Patients. J Kartal TR 2016;27(1):37-41
11. Algara M, Rodríguez N, Viñals P, Lacruz M, Foro P, Reig A et al. Prevention of radiochemotherapy-induced esophagitis with glutamine: results of a pilot study. Int J RadiatOncolBiolPhys2007;69:342-9
12. Choi K, Lee SS, Oh SJ, Lim SY, Lim SY, Jeon WK et al. The effect of oral glutamine on 5-fluorouracil /leucovorininducedmucositis/stomatitis assessed by intestinal permeability test. ClinNutr2007;26:57-62
13. White J, Tai A, Arthur D, Buchholz T, MacDonald S, Marks L et al. Radiation Therapy Oncology Group. Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions.2014
14. Early breast cancer trialistscolloborative group(EBCTCG). Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M et al.Effects of radiotherapy after breast-conserving surgery on 10 year recurrence and 15 year breast cancer death:metaanalysis of individiual patient data for10.801 women in 17 randomised trials. Lancet 2011;378(9804):1707-16
15. Huang EY, Leung SW, Wang CJ, Chen HC, Sun LM, Fang FM, et al. Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. Int J RadiatOncolBiolPhys2000;46:535-9
16. Barlett DL, Charland S, Torasian MH. Effects of glutamin on tumor and host growth. Ann SurgOncol1995;2:71-6
17. Eda K, Uzer K, Murat T, Cenk U.The effects of enteral glutamine on radiotherapy induced dermatitis in breast cancer. Clin Nutr. 2016 Apr;35(2):436-439
18. Stachowicz-Stencel T, Synakiewicz A. Glutamine as a supplemental treatment in pediatric and adult oncology patients. Expert OpinInvestig Drugs 2012;21:1861-71
19. Peterson DE, Jones JB, Petit RG. 2nd. Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. Cancer 2007;109:322-31
20. Topkan E, Parlak C, Topuk S, Pehlivan B. Influence of oral glutamine supplementation on survival outcomes of patients treated with concurrent chemoradiotherapy for locally advanced non-small cell lung cancer. BMC cancer 2012;12:502
21. Etiz D, Bayman E, Akcay M, Sahin B, Bal C. Dosimetric and clinical predictors of acute esophagitis in lung cancer patients in Turkey treated with radiotherapy. Asian PacJ Cancer Prev2013;14:4223-8
22. Zhang Z, Xu J, Zhou T, Yi Y, Li H, Sun H, et al. Risk factors of radiation-induced acute esophagitis in non-small cell lung cancer patients treated with concomitant chemoradiotherapy. RadiatOncol2014;9:54
23. Lopez-Vaquero D, Gutierrez-Bayard L, Rodriguez-Ruiz JA, Saldaña-Valderas M, Infante-Cossio P**.** Double-blind randomized study of oral glutamine on the management of radio/chemotherapy-induced mucositis and dermatitis in head and neck cancer. MolClinOncol. 2017 Jun;6(6):931-936
24. Harper JL, Franklin LE, Jenrette JM, Aguero EG. Skin toxicity during breast irradiation: pathophysiology and management. South Med J. 2004 Oct;97(10):989-93
25. Knox WE, Horowitz ML, Friedell GH. The proportionality of glutaminase content to growth rate and morphology of rat neoplasms. Cancer Res. 1969:26;29(3):669-80