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A Phase III Randomized Clinical Trial Study of Chemoradiation using Lovastatin/Cisplatin in Patients with Head and Neck Squamous Cell Carcinoma

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Abstract

Background: Target therapy of apoptosis signaling has been previously shown to have a therapeutic role in the treatment of head and neck squamous cell carcinoma (HNSCC). The present study aimed to investigate the safety and maximum dose of Lovastatin (80 mg/day) in additional standard therapy with cisplatin.

Method: The current study is a phase III randomized clinical trial, conducted to determine the effect of Lovastatin on HNSCC. To eliminate the interference effect of previous treatments and surgeries, newly-diagnosed HNSCC patients were included. A total of 45 patients from May 2017 to February 2018 were enrolled. The intervention group received Lovastatin/cisplatin chemoradiotherapy and the control group received only cisplatin. All the subjects were evaluated on a weekly basis during the treatment and three and six weeks after that for related adverse events (AEs). The response rate to the treatment was assessed eight weeks following the treatment.

Results: No significant differences were found between the two groups concerning the objective response (OR) rate (95.8% vs. 95.2%, $P = 1$, 95% confidence interval). In the intervention group, tumors were entirely removed in 70.8% of the subjects and partial response was seen in 25% of them. No patient was excluded due to the AEs. The gastrointestinal AE (31.1%) was the most frequent one.

Conclusion: In the present study, comparing the intervention and control groups, no significant differences were observed concerning OR, but unlike previous investigations, the related cardiac AEs were not seen. This observation confirmed the hypothesis that there is a possible association of Lovastatin use with better OR compared with standard chemoradiation (cisplatin) in the initial point of the treatment. However, further research is needed to investigate different doses of Lovastatin with longer follow-ups and new diagnoses of HNSCC patients.

Keywords: Carcinoma, Squamous cell, Chemoradiation, Cisplatin, Lovastatin

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is known as one of the most commonly squamous cell carcinomas, particularly in developing countries in which the patients are younger (below 50).[1,2] Since HNSCC is categorized as the immunosuppressive cancers, second primary malignancies are a primary concern after the treatment.[3] Surgery, chemotherapy, and radiotherapy are the first-line treatments for locally advanced HNSSC. For greater efficacy, cisplatin, the most common drug in chemotherapy, is co-administered with radiotherapy. The standard regimen of cisplatin is 100 mg/m^2 every three weeks concurrent with radiotherapy; however, after evaluating the effectiveness and complications, in some centers, the three weekly schedule changes to a weekly regimen.[4-6]

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes the conversion of HMG-CoA into mevalonate, which is an essential step in the biosynthesis of cholesterol in the liver.[7] The products of this process are involved in cellular functions, including membrane integrity, protein synthesis, and apoptosis.[8] HMG-CoA reductase inhibitors or statins are one of the most important classes of antilipemic drugs that reduce low-density lipoprotein (LDL) cholesterol levels.[7] Statins administration, like Lovastatin, reduces atherosclerotic plaque formation and the incidence of cardiovascular morbidity and mortality related to invasive cardiovascular, non-cardiovascular procedures, and surgeries.[9,10] Additionally, several investigations have revealed that Lovastatin has antitumor activity via anti-proliferative, antiangiogenic, and antimetastatic properties.[7,11,12] Lovastatin, by targeting HMG-CoA reductase, results in the production of some mediators. These agents induce apoptosis by mevalonate metabolite through activating ATF-family of transcription factors involved in regulation of several genes.[13] One of the most essential characteristics and mechanisms of HNSSC is its resistance against apoptosis.[14] Therapeutic targeting of this pathway could affect the carcinogenesis process. The apoptotic response of Lovastatin has been observed in HNSCC and thyroid cancer susceptible cell lines.[15,16]

These therapies are not without side-effects. In this regard, we can mention the reduction in the delivered dose, which is due to weight loss and atrophy.[17] One dose-limiting toxicity of Lovastatin in patients with solid tumors is myopathy, which can be the result of the side-effects. In the current survey, to address this possible interference, only newly-diagnosed HNSCC patients were selected for evaluating the effectiveness of co-administration of Lovastatin and chemoradiation therapy.

Material and Methods

Study design

The current survey is a single-center, phase III clinical trial that compared the effect of co-administration of Lovastatin with cisplatin to standard chemoradiotherapy with cisplatin in newly-diagnosed HNSCC patients. We recruited the study subjects from the department of radiotherapy and oncology at Ahvaz Golestan Hospital, Ahvaz, Iran, between May 2017 and February 2018. The Medical Ethics Committee of Jundishapur Ahvaz University approved the current work (Reference number: IR.AJUMS.REC.1396.900), which was performed as a phase III clinical trial (IRCT code: 20171204037739N1).

Study population

In this parallel-group trial, 45 newly-diagnosed patients with HNSCC were randomly divided into the intervention and control groups. The intervention group received Lovastatin in addition to standard chemoradiation with cisplatin. The inclusion criteria for selecting the patients were as follows: age ≥18 with histological or pathological HNSCC diagnosis, any primary sites, and both genders. All the patients had unrespectable tumors. The exclusion criteria were considered as the history of surgery and mass resection, sensitivity to Lovastatin, patients with distant metastatic disease, pregnancy, metastatic disease, receiving chemotherapy before starting chemoradiotherapy, the life expectancy of less than two years, the presence of liver or renal

Table 1. Patients' demographic and clinical information

Variable	Intervention (n=24)	Control (n= 21)	*P*-Value
Age (Mean ± SD)	57.29 ± 13.78	56.05 ± 12.6	0.75
Gender			
Male	18 (75%)	14 (66.7%)	0.53
Female	6 (25%)	7 (33.3%)	
Primary Tumor Location			0.43
Nasopharyngeal	3 (12.5%)	5 (23.8%)	
Non-nasopharyngeal	21 (87.5%)	16 (76.2%)	
Larynx	13	11	
Hypopharynx	3	2	
Anterior Tongue	3	2	
Base of tongue	2	1	
Stage			
Stage II (T2N1)	3 (12.5%)	2 (9.52%)	0.52
Stage III (T2N2/T3N1, N2)	14 (58.33%)	11 (52.38%)	
Non-metastatic Stage IV (T4, any N M0/ any T, N3 M0)	7 (29.17%)	8 (38.1%)	
Initial laboratory tests			
Hemoglobin (g/dL)	12.1 ± 1.3	12.3 ± 1	0.31
White blood cell (in mm3)	6120 ± 1230	6045 ± 1450	0.23
Platelet (in mm3)	265000 ± 110000	255000 ± 100000	0.87
Creatinine (mg/dL)	1.1 ± 0.1	1.2 ± 0.2	1.02
Aminotransferase (U/L)	22 ± 3	21 ± 4	1.32
Initial lipid profile			
Total cholesterol (mg/dL)	185 ± 33	190 ± 20	0.62
Low density lipoprotein (mg/dL)	145 ± 10	140 ± 15	0.54
High density lipoprotein (mg/dL)	42 ± 5	45 ± 10	1.54
Triglycerides (mg/dL)	160 ± 34	165 ± 30	1.01

SD: Standard deviation

dysfunction that prevented chemotherapy or prescription of Lovastatin, and receiving medications including anti-inflammatory drugs, like aspirin, more than three days a week, anticoagulants, fibrates, cyclosporine, and oral contraceptives.

All the subjects with stage III in this trial had nasopharyngeal carcinoma; for these patients, chemoradiation was used, which is the standard treatment. There were two patients with nasopharyngeal carcinoma in the control group with stage III; they underwent chemoradiation as the standard therapy. Those with laryngeal carcinoma, who were candidates for total laryngectomy, and those with hypopharyngeal carcinoma at stage III, who did not accept the surgery due to possible post-operation complications, underwent chemoradiation as a definitive treatment.

There were not any cases with anterior tongue SCC at stage III in this trial. All the anterior tongue cases were at stage IV non-metastatic disease.

Treatment discontinuation was considered as a failure to complete at least five weekly chemotherapy sessions or not completing radiotherapy in both groups. The eligible patients were randomly divided into two groups of intervention (n=24) and control (n=21). All the patients signed the informed written consent before the start of the study.

Treatment

All the cases herein received definitive chemoradiation therapy based on weekly schedules as follows: intravenous cisplatin (40 mg/m^2) combined with one-liter normal saline over two hours on days 1, 8, 15, 22, 29, 36, and 43 during the radiotherapy period (7 weeks) and a total dose of 70 Gy with 2 Gy daily fractions for 7 weeks by 3-dimensional conformal radiation

Table 2. Acute hematological AEs in the two groups

Complications	Intervention (n=24)	Control (n= 21)	*P*-Value
Anemia			
Normal hemoglobin (>10g/dL)	19 (79.16%)	18 (85%)	0.70
<Grade 3 (8-10g/dL)	5 (20.84%)	3 (15%)	
≥Grade 3 (<8g/dL)	0	0	
Leukopenia			
Normal leukocyte (>4000/mm^3)	18 (75%)	16 (76.16%)	0.92
<Grade 3 (2000-4000/mm^3)	5 (20.83%)	4 (19%)	
≥Grade 3 (<2000/mm^3)	1 (4.16%)	1 (4.79%)	
Thrombocytopenia			
Normal Platelet (>100000/mm^3)	21(87.5%)	20 (95.23%)	0.61
<Grade 3 (50000-100000/mm^3)	3 (12.5%)	1 (4.76%)	
≥Grade 3 (<50000/mm^3)	0	0	

AEs: Adverse events

therapy using a linear accelerator. The total dose to gross tumor volume (including primary tumor and gross lymphadenopathy) was 70 Gy and the dose of the spinal cord was kept below the tolerance dose by excluding the spinal cord from the radiation field after 44 Gy. The total daily dose (80 mg /day) of Lovastatin was divided into two doses in the intervention group. Prophylactic medications were not supplied.

Assessment

The treatment response was assessed based on the revised response evaluation criteria in solid tumors (RECIST) guideline version 1.1.[18] According to the treatment response, the patients were divided into four groups, namely complete response (CR), partial response (PR), progression response, and stable response. The objective response rate (ORR) was considered as favorable response to treatment, which was defined by the existence of CR and PR simultaneous. ORR and AEs were the main objectives of the current survey, but CR and PR were evaluated as well. Eight weeks after the treatment, the AEs and response to the treatment were assessed, in which the refractory to the treatment and AEs were observed.

The sizes of the tumor and lymph nodes were measured and recorded before and after the treatment. To measure the radiological response, a spiral computed tomography (CT) scan of head and neck with a slice thickness of up to 5 mm was performed for all the patients prior to the treatment and eight weeks following the completion of chemoradiation therapy. All the subjects were evaluated by the partner assistants of this study in a weekly visit schedule during the treatment course. Adverse events (AEs) of the treatment, including hematological, kidney, and liver toxicity, were monitored every 7 days during the treatment period and in the third and sixth weeks after the treatment, according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) guideline version 4.02.[19] According to this guideline, the interruption treatment was done in grade 3 or severe AEs related to grade 0 to 1. The treatment was discontinued in grade 4 and unresolved grade 3 AEs within 12 weeks after the last treatment dose.

Statistical analysis

Chi-square and Fisher's exact tests were used to determine the relationship between qualitative variables between the case and control data. The odds ratio (OR) with a 95% confidence interval (CI) was calculated. Unconditional logistic regression analysis was utilized to control the possible confound in factors. *P*-value < 0.05 was considered to be significant. All the data were analyzed via SPSS software (V24).

Result

Patients

45 newly-diagnosed HNSSC patients were recruited for this study, out of whom, 71.1% were male and 28.9% were female. There was no exclusion after randomization in any of the groups.

Table 3. Acute non-hematological AEs in the two groups

Complications	Intervention (n=24)	Control (n= 21)	*P*-Value
Dermatitis			
<Grade 3	24 (100%)	21 (100%)	1.11
≥Grade 3	0	0	
Oral mucositis			
<Grade 3	3 (12.5%)	6 (28.57%)	0.87
≥Grade 3	5 (20.83%)	5 (23.8%)	
Pharyngitis			
<Grade 3	24 (100%)	21 (100%)	1.00
≥Grade 3	0	0	
Nausea and vomiting			
<Grade 3	10 (41.66%)	4 (19.04%)	0.10
≥Grade 3	0	0	
Fever			
<Grade 3	1 (4.16%)	1 (4.76%)	1.05
≥Grade 3	0	0	

AEs: Adverse events

The mean age in both groups was approximately 56 years old (Table 1). Out of the initial 45 samples, 12.5% (3) had nasopharyngeal carcinoma and 87.5% (21) had non-nasopharyngeal carcinoma (Table 1). Table 1 represents the primary site of tumor location in non-nasopharyngeal cancers. We evaluated all the patients for the stage of disease; the result showed that 55.5% (25) were in stage III, followed by 33.3% (15) in stage IV and 1.1% (5) in stage II (Table 1). The cases with distance metastasis were not considered as stage IV. Before commencing the treatment, we assessed the hematological parameters and liver function (Table 1).

Safety

The median follow-up duration was 12 months. During the entire treatment period, all the patients received complete treatment and none of them were excluded due to the AEs. After evaluating the patients for hematological AEs, no significant differences were found between the two groups (Table 2). ≥ Grade 3 leukopenia was observed only in one patient in each group. ≥Grade 3 anemia and ≥grade 3 thrombocytopenia were not found in the groups (Table 2). ≥Grade 3 non-hematological AEs were not detected in any patients (Table 3). All the subjects experienced treatment-related grade 1 and 2 of pharyngitis and dermatitis (Table 3). Afterwards, the gastrointestinal (31.1%) was the most frequent AE. The myopathy, hypersensitivity, neutropenic fever, liver, and kidneys AEs were not detected in the patients. There were no treatment-related deaths.

Efficacy

Out of all the 45 initial patients, 66.6% (30) achieved a CR, 28.8% (13) achieved a PR, and 4.6% (2) experienced progressive disease. The ORR, which is defined as the sum of CR and PR, was 95.8% (23) in the intervention group and 95.2% (20) in the control group. This finding showed no significant differences in achieving CR ($P = 0.526$, 95% CI) and ORR ($P = 1$, 95% CI) between the two groups (Table 4). In each group, one patient showed progressive disease and stable response was not seen (Table 2).

Discussion

45 patients were evaluated for efficacy and safety of Lovastatin. Our results have shown there is no exclusion from the study due to the AEs. Also, there were no treatment-related deaths. The most frequent treatment-related AEs were grade 1 and 2 of pharyngitis, dermatitis, and gastrointestinal, which were not significant between the two groups. Our findings revealed that the tumor was entirely removed in 70.8% (17 patients) and PR was seen in 25% (6) of the intervention group. Compared with the control group, with 61.9% (13 patients) complete removal of tumors, there

Table 4. Treatment response based on the revised RECIST* guideline version 1.1

Criteria	Intervention (n=24)	Control (n= 21)	*P*-Value
Complete response	17 (70.8%)	13 (61.9%)	0.52
Partial response	6 (25%)	7 (33.3%)	
Stable disease	-	-	-
Progressive disease	1 (4.2%)	1 (4.8%)	1.23
Objective response	23 (95.8%)	20 (95.2%)	1.03

*RECI ST: Response evaluation in solid tumors

were no significant differences between the groups.

This is in accordance with Tsai.HK and Katz. MS et al. who reported that statins can improve local control of bladder carcinoma and CR in rectal cancer.[20,21] CR, without any life-threatening AEs in the intervention group, showed that Lovastatin may have therapeutic roles in HNSCC treatment.

Lovastatin prevents the effect of the injury from cisplatin on tubular epithelial cells and oral mucous membranes, which are the frequent AEs of cisplatin.[22,23] This is in accordance with our finding that oral mucositis was more frequent in the control group (28.5% vs.12.5%). The most frequent AEs in the intervention group were the gastrointestinal ones, the differences were statistically insignificant. Prophylactic drugs are prescribed to prevent muscle weakness in patients. In the present study, the administration of prophylactic drugs was avoided to better understand the effect of Lovastatin.

Similar to other cancers, resistance to apoptosis and inhibition of apoptosis signaling is the main evasion and survival of HNSCC. Among the genes mutated in apoptosis pathway signaling, the role of *TP53*, P21, P27, and CKN2A RhoA is well established in HNSCC carcinogenesis.[1,24,25] RhoA is a member of the Rho family, which mediates cell growth, apoptosis, transcriptional regulation, and membrane trafficking.[26] RhoA, by affecting signaling transcription factors, promotes apoptosis, metastasis, and transformation in cancers.[26] It was demonstrated statins, specifically Lovastatin, in addition to lowering cholesterol and preventing the incidence of cardiovascular disease, has anti-tumor activity.[27-30] Lovastatin, by enhancing the activation of apoptotic genes, such as *TP53*, RhoA, and P21, promotes apoptosis in squamous cell carcinoma.[13,25] Although there has been increasing clinical trial evidence suggesting that statins might have a therapeutic effect on solid tumors,[31,32] there are no published data about the possible role of statins in newly diagnosed locally advanced cases. Thus, we conducted this study to compare the efficacy and safety of a fixed-dose of Lovastatin (80 mg/day) in addition to the chemoradiotherapy to cisplatin in patients with newly-diagnosed HNSCC. The maximum recommended dose of Lovastatin is 80 mg/day for the cholesterol-lowering effect. In the current work, based on previous clinical trial studies, Lovastatin dose equaled the maximum dose administered in patients with cardiovascular diseases, which was significantly lower than the safe level determined by the study of Knox et al.[33]

In a phase I trial study conducted by Knox JJ et al., 23% of patients with recurrent or metastatic HNSCC or cervix cancer experienced stable disease for more than three months after the administration of Lovastatin; meanwhile, myopathy was dose-limiting toxicity.[33] It is in agreement with Thibault A et al. who reported that myopathy is one of the main dose-limiting toxicities.[34] A possible explanation for this is the reduction in ubiquinone, an end-product of the mevalonate pathway, which may be associated with myopathy.[33] This is in contrast to our findings which indicated that none of the patients experienced myopathy. This shows that the dose of Lovastatin applied herein was effective. It could be explained through the fact that Knox JJ et al. and Kim WS et al. evaluated every patient with recurrent or even metastatic HNSCC and solid tumors; whereas in the current study, only newly-diagnosed locally advanced HNSCC cases

were included. Therefore, other treatments and AEs influence the effective dose of Lovastatin. This combination of findings provides support for the conceptual premise that using Lovastatin should be considered in the treatment of HNSCC.

The main limitation of current study is the assessing just one dosage of Lovastatin, hence, further investigations with different doses of Lovastatin, longer follow-ups, and a bigger sample size could be suggested.

Conclusion

The main prominent finding in the present clinical trial, is that unlike previous investigations, the related cardiac AEs were not seen; this may be due to the use of Lovastatin in the initial treatment, in which there were not any drug or AEs conflictions. This observation may support the hypothesis that there is a possible association between Lovastatin use and better OR compared with standard chemoradiation with cisplatin in the initial point of treatment. Also, our results have demonstrated that Lovastatin is not accompanied with any treatment-related, so it is worthwhile to do more studies in this regard.

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Conflict of Interest

None declared.

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