International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Use of Geftinib and Methotrexate in Residual Cases of Squamous Cell Carcinoma of Head and Neck after Radical Treatment

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Abstract: ***HNSCC is one of the leading cancers in India. There is very limited treatment option for residual cases of HNSCC after radical treatment. We have tried Gefitinib and methotrexate combination for residual disease after radical treatment.125 patients who have residual disease at primary site after 6 weeks of completion of radical treatment were started on gefitinib 250mg daily and methotrexate 15 mg weekly. Treatment was given for 6 months with monthly follow up and toxicity assessment. After that response to treatment was assessed. Patients with CR, PR, SD and PD are 9.3, 22.9, 30.2 and 28.1 percent respectively. So, such group of patients can be started on gefitinib and methotrexate with durable response and manageable toxicity***

Keywords: Gefitinib, Methotrexate, HNSCC, Residual disease

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the leading cancers in India accounting for 23 percent of all cancer in males and 6 percent in females. Most cases (80%) present in advanced stages and survival is poor with all modalities of treatment[1]. These patients have poor prognosis with median survival in range of 6–12 months[2]. Treatment options are limited for residual/recurrent/metastatic disease, only few patients are eligible for surgery or re - irradiation. Palliative treatment is considered as standard of care in these patients. Platinum based regimen with 5 - FU is often considered as standard in patients with good performance status[3 - 5]. Addition of taxane resulted in higher response rate of 20 to 43%[6]. As most of these patients present with poor general health or had received prior platinum - based chemotherapy, methotrexate as a single agent remains a drug of choice in a significant proportion of patients[7].

EGFR is a member of the family of tyrosine kinase receptors that is overexpressed in more than 90% of head and neck squamous cell carcinomas (HNSCC) [8]. Dysfunction of this receptor and its associated pathways tend to have significant implications for the susceptibility and prognosis of head and neck cancer[9]. Gefitinib, an EGFR tyrosine kinase inhibitor has shown promising results showing response rate and median survival of 10.6%–1.4% and 8.1 months - 5.5 months at a dose of 500 mg/ 250 mg daily respectively[10 - 12].

Due to Limited resources, advanced presentation of disease, lack of expertise for surgical intervention and non - availability of advanced RT technique, primary treatment as well as treatment of residual disease affected badly. Keeping all above factor in mind, we have tried oral methotrexate and gefitinib for treatment of such patients with residual disease after radical treatment.

Aim

To evaluate efficacy and toxicity of gefitinib and methotrexate in cases of residual disease of head and neck cancer after radical treatment

2. Material and Method

The retrospective analysis was done from case record of residual case of squamous cell carcinoma head and neck receiving gefitinib and methotrexate from January 2020 to December 2020 at JNMCH AMU Aligarh. From the case record total 285 patients had residual disease either at primary, nodal or nodal plus primary site during this period by radiological evaluation at 8 weeks of treatment after receiving full course of radiotherapy with concurrent weekly cisplatin. A total of 125 patient out of 285 were selected who had residual disease only at primary site and were unable to tolerate more aggressive treatment. These patients are put on weekly 15 mg methotrexate along with gefitinib 250mg daily. Patients follow up and toxicity assessment was done

monthly. By the end of 6 - month clinicoradiological evaluation was done and RECIST 1.1 criteria were used to evaluate the response to therapy and patients were grouped as complete response (CR), no evidence of disease; partial response (PR), more than 30% reduction in sum of the maximum diameter; progressive disease (PD), increase in more than 20% size from the minimum measured disease; and stable disease (SD). Overall response rate was defined as CR + PR and clinically meaningful response was defined as CR + PR + SD. Toxicity to treatment is assessed by using common toxicity criteria version 3.

Treatment Protocol

1) Tab gefitinib 250 mg once daily
2) Tab methotrexate 15mg weekly

Blood parameters are checked before commencement of treatment and on monthly follow up

Patients Characteristics

1. Patient number	125
2. Age	35 - 65
3. Male/Female	96/29
4. Smoker/Non smoker	90/35
5. Primary tumor site	
a. Oropharynx	82
b. Oral cavity	26
c. Larynx	17
6. Histology	
a. Squamous cell carcinoma	125
b. Others	
7. Initial stage	
a. Stage 1	0
b. Stage 2	3
c. Stage 3	37
d. Stage 4	85

Response to treatment

Primary Disease	No. of Patients	Percentage
Complete response	9	9.3
Partial response	22	22.9
Stable disease	29	30.2
Progressive disease	27	28.1
Death during treatment	9	9.3
Overall response rate (CR+PR)	31	32.2
Clinically meaningful response (CR+PR+SD)	60	62.5

3. Result

A total of 728 patients of head and neck cancer were registered during this period at our center. Out of which 98 patients were defaulted and 630 patients received either radical or palliative treatment. A sum of 125 patients found to have residual disease only at primary site who are not eligible for other form of radical treatment were started on 15 mg weekly Methotrexate and 250 mg daily Gefitinib. The number of male patients being higher than the female patients is in agreement with published Indian Literature. Majority of the patients had oropharynx followed by oral cavity as primary disease site.8 patients were defaulted and 21 patients were not compliant to treatment so they were excluded from analysis. Most of the patient received prior platinum - based chemotherapy either in neoadjuvant or concurrent setting. Majority of patients were having stage IV disease. Most of the patient completed 6 months of treatment with monthly follow up after that CECT was done for the evaluation of treatment response.

Responses to therapy were summarized in above table.9.3% patients achieved complete response, 22.9% patient achieved partial response, 30.2% patients had stable disease, 28.1%patients had progressive disease while 9 patients died during treatment. These deaths are not due to toxicity but it was related to disease itself.

Toxicity

Toxicities observed during treatment are summarized in the Table below. Monthly follow up was done to assess toxicities and most frequently encountered toxicities were in Grade 1 or 2 in Severity. The most common toxicity reported was rash, diarrhea, nausea - vomiting, mucositis, thrombocytopenia and leucopenia. no grade 3 or grade 4 toxicity were observed. Most common reason for interruption of treatment is diarrhea which was not more than a week. Monthly blood investigations were done to assess hematological toxicities.

Toxicity Assessment

	Grade 1	Grade 2	Grade 3	Grade 4
Rashes	28	28	0	0
Nausea/Vomiting	22	22	0	0
Mucositis	16	16	0	0
Diarrhea	13	13	0	0
Anemia	5	5	0	0
Leucopenia	8	8	0	0
thrombocytopenia	6	6	0	0

4. Discussion

Retrospective study was done at our Centre to assess the efficacy in terms of response rate and toxicity of combined methotrexate and gefitinib in residual cases of head and neck cancer. Post radical treatment if it comes to be residual disease there are very limited treatment options. The standard treatment in such cases is intravenous chemotherapy with cisplatin and 5FU or platinum with taxane. Intravenous methotrexate is also helpful in such cases. Most of the patient who present to our center are of lower socioeconomic status with compromised nutritional status and after getting radical treatment in form of CRT or surgery followed by RT/CRT patients are not in position of taking intravenous chemotherapy because of poor GC. The limited treatment options, high morbidity, treatment - related toxicities, high incidence of recurrences, as well as increased cost of therapy makes clinician think about some cost effective and tolerable treatment. There is recent shift in treatment which focus on disease stabilization and quality of life instead of cure. Gefitinib has promising role in recurrent/metastatic HNSCC in terms of median overall survival and progression free survival of 6 months and 3 months respectively[13, 14]. The recent reviews and meta - analysis showed that methotrexate is still an option in head and neck squamous cell carcinoma in terms of disease control and in maintaining QOL[15]. On the basis of these results, we have given methotrexate and gefitinib in combination considering the fact that they also have

different toxicity profile. In this study overall response rate is 25 % which is comparable to kirby et at. overall response rate of 36%. Stable disease is 30% which also comparable with this study (kirby et el., stable disease 26 %). CR +PR+SD is 60 %in our study which lower than Anuradha et at., who reported it at 80% in Indian population. CR is slightly higher in our study which might be due to false positive initial imaging in case of carcinoma larynx.

5. Conclusion

On the basis of above result it can be said that patients with residual disease in head and neck cancer after radical treatment can be started on gefitinib and methotrexate with durable response and manageable toxicity.

References

[1] Al - Sarraf M. Treatment of locally advanced head and neck cancer: historical and critical review. Cancer Control 2002; 9: 387 - 99; PMID: 12410178

[2] Brockstein BE. Management of recurrent head and neck cancer: recent progress and future directions. Drugs 2011; 71: 1551 - 9; PMID: 21861540; http: //dx. doi. org/10.2165/11592540 - 000000000 - 00000

[3] Jacobs C, Lyman G, Velez - Garcia E, Sridhar KS, Knight W, Hochster H, Goodnough LT, Mortimer JE, Einhorn LH, Schacter L, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol.1992; 10: 257 - 63; PMID: 1732427

[4] Forastiere AA, Mitch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, Kish JA, McClure S, VonFeldt E, Williamson SK, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck: A Southwest Oncology Group Study. J Clin Oncol.1992; 10: 1241 - 51; PMID: 1634913

[5] Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol.2005; 23: 8646 - 54; PMID: 16314626; http: //dx. doi. org/10.1200/JCO.2005.02.4646

[6] Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol.2010 Oct; 21 Suppl7: vii252 - 61. doi: 10.1093/annonc/mdq453. PMID: 20943624.

[7] Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol.2006; 24: 2644 - 52; PMID: 16763278; http: //dx. doi. org/10.1200/ JCO.2005.05.3348

[8] Kalyankrishna S, Grandis JR: Epidermal growth factor receptor biology in head and neck cancer. J Clin Oncol.2006, 24: 2666 - 72.10.1200/JCO.2005.04.8306

[9] Ang KK, Andratschke NH, Milas L: Epidermal growth factor receptor and response of head - and - neck carcinoma to therapy. Int J Radiat Oncol Biol Phys.2004, 58: 959 - 65.10.1016/j. ijrobp.2003.07.010

[10] Cohen EE, Rosen F, Stadler WM, Recant W, Stenson K, Huo D, Vokes EE. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2003; 21: 1980 - 7; PMID: 12743152; http: //dx. doi. org/10.1200/ JCO.2003.10.051

[11] Cohen EE, Kane MA, List MA, Brockstein BE, Mehrotra B, Huo D, Mauer AM, Pierce C, Dekker A, Vokes EE. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res 2005; 11: 8418 - 842; PMID: 16322304; http: //dx. doi. org/ 10.1158/1078 - 0432. CCR - 05 - 1247

[12] Kirby AM, A'Hern RP, D'Ambrosio C, Tanay M, Syrigos KN, Rogers SJ, Box C, Eccles SA, Nutting CM, Harrington KJ. Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. Br J Cancer.2006; 94: 631 - 6; PMID: 16495923

[13] Wheeler RH, Jones D, Sharma P, Davis RK, Spilker H, Boucher K, et al. Clinical and molecular phase II study of gefitinib in patients (pts) with recurrent squamous cell cancer of the head and neck. Proc Am Soc Clin Oncol 2005; 23: 507s.

[14] Stewart JS, Cohen EE, Licitra L, Van Herpen CM, Khorprasert C, Soulieres D, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. J Clin Oncol 2009; 27: 1864 - 71.

[15] Hotte SJ, Wright JR. Understanding the results of meta - analyses in the treatment of head and neck squamous cell cancer. Hematol Oncol Clin North Am 2008; 22: 1257 - 66