Research Article

GST (Gefitinib as Salvage Treatment) in Pretreated Head and Neck Squamous Cell Cancer

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Abstract

Purpose: To determine the efficacy and safety profiles of GST (gefitinib as salavage therapy) in patients with advanced recurrent, residual and/or metastatic squamous cell cancer of the head and neck (HNSCC).

Subjects and Methods: Patients with recurrent, residual, or metastatic (R/R/M) HNSCC, were treated with gefitinib 250mg orally daily for 3 weeks.

Results and Conclusion: Partial response (PR) was noted in 10% of patients, median progression free survival (PFS) was 3.3 months. Anemia was observed in 16.7% of patients, toxicity related to total leucocyte count grade I,II &III toxicities were observed in 20%, 3.3% and 0%. Only grade I hepatic toxicity was observed in 20%. No case of renal toxicity was seen. Grade I-II upper gastrointestinal toxicity (nausea/ vomiting) was noted in 13.3% patients. Lower gastrointestinal toxicity (diarrhea) was observed in 46.7% of patients. Skin rash was graded and 8 (26.7%) patients demonstrated skin reactions. Overall survival (OS) was 4 months. Gefitinib was well tolerated in this heavily pretreated HNSCC population and produced prolonged disease stabilization.

Keywords: Gefitinib; Palliative; Head and neck cancer; Chemoradiation

1. Introduction

Worldwide incidence carcinoma of head and neck region in 2012 were 599,637 which was 4.2% of all cancers. Deaths due to carcinoma of head and neck were 324,834 which was 4% of all cancers [1]. In India alone, 2.5 lakhs new patients are diagnosed every year, of whom about 70% are in an locally advanced stage [2]. Carcinoma of head and neck is one of the commonest malignancies in India and is responsible for 22.9% of cancer related mortality [3].

Approximately 70-80% of these patients are diagnosed with locally advanced disease [4]. Chemoradiation is most preferrable treatment for LAHNC [5, 6]. Local failure rate is high in the range of 60-70%. These patients carry limited prognosis and are suitable for palliative treatment. Palliative treatment is based on many considerations such as borderline performance status (PS), existing co-morbidities, etc [7]. Combination chemotherapy is more effective than single agent chemotherapy but is sometimes not tolerated by patients because of poor nutritional status and general condition of the patients. In view of above, we enrolled thirty patients in this study and they received gefitinib as salvage therapy (GST) in HNSCC.

2. Material and Methods

Thirty Patients with histologically or cytologically proven diagnosis of locally R/R/M HNSCC from any of the primary sites were candidates for this study who were pretreated (had surgery and/or radiation therapy with/without concomitant chemotherapy). Patients were enrolled for the study after obtaining informed written consent. All patients received Gefitinib 250 mg daily for 3 weeks. Tumor assessment was done by consistent clinical examination after 3 weeks of starting therapy and commencement of next cycles for 6 cycles.

3. Results

Partial response (PR) was noted in 10% of patients, median progression free survival (PFS) was 3.3 months. Anemia was observed in 16.7% of patients, toxicity related to total leucocyte count grade I,II &III toxicities were observed in 20%, 3.3% and 0%. Only grade I liver toxicity was found in 20%. No case of renal toxicity was seen. Grade I-II upper gastrointestinal toxicity (nausea/ vomiting) was noted in 13.3% patients. Lower gastrointestinal toxicity (diarrhea) was observed in 46.7% of patients. Skin rash was graded and 8 (26.7%) patients demonstrated skin reactions. Overall survival (OS) was 4 months.

4. Discussion and Conclusion

Epidermal growth factor receptor (EGFR) , is a transmembrane glycoprotein whose intracellular domain has tyrosine kinase activity. EGFR is involved in in the regulation of cell cycle progression, inhibition of apoptosis, angiogenesis, tumor cell invasion and metastasis. Gefitinib is an inhibitor of tyrosine kinase that blocks the pathway of signal transduction [8]. EGFR is overexpressed in 85% to 95% HNSCC [8]. Gefitinib in a dose dependent manner has been shown to disrupt cell cycle progression [9].

Baselga et al studied Gefitinib in 28 patients with HNSCC (Total no. of patients=250). Gefitinib in the range 150-800 mg was was favorably tolerated. The most common toxicities reported were diarrhea (47-55%), asthenia (44%) and acnieform follicular rash (46-64%). Stable disease was achieved in 50% of patients HNSCC [10]. In a phase 2 study by Cohen et al, evaluated oral Gefitinib (500 mg /day) in 52 patients with R/R/M HNSCC. The objective PR rate of 10.6% was seen. 3.4 and 8.1 months were the median time to progression and death and an estimated 1 year survival of 29%. Only a single case of grade 4 toxicity (hypercalcemia), a 4-6% of grade 3 toxicity (anorexia, diarrhea, nausea), 48% patients developed grade 1 or 2 cutaneous rash [11].

Athnassios et al randomly assigned patients with R/R/M SCCHN to receive weekly Docetaxel plus either placebo (arm A) OR Gefitinib 250mg/day orally (arm B) until disease progression. The study was closed early after 270 patients were enrolled and an interim analysis was done (arm A, n=136, arm B, n=134). Median OS was 6 months in arm A vs 7 months in arm B, further careful analysis showed that Gefitinib improved survival in patients lessr than 65 years old [12].

Belon et al have investigated Gefitinib together with Docetaxel based regimens for the treatment of SCCHN. The addition of Gefitinib to the well established taxanes and platinum regimen was investigated in phase 2 trial in 23 patients with recurrent residual and metastatic SCCHN. In this trial, the half of the patients shown PFS of 5.1 months. Safety analysis demonstarted as, grade 3/4 toxicities including neutropenia (41.2% of patients, including 23.5% with febrile neutropenia), anemia (17.7%), asthenia (11.8%) and diarrhea, vomiting, anorexia, and leucopenia (5.9% each) [13].

Vermorken et al. conducted a randomized phase III trial large number of (n=482) patients with R/R/M-SCCHN, refractory to platinum or not suitable for platinum based therapy, were divided in 3 groups to receive either tablet Gefitinib 250 mg/day or 500 mg/day or t methotrexate 40 mg/m^2 i.v. weekly. Neither Gefitinib 250 mg/day nor Gefitinib 500 mg/day has shown benefit in survival in relation with i.v methotrexate. Overall Response rates were 2.7%, 7.6% and 3.9%, respectively and median OS was 5.6, 6 and 6.7 months, respectively [14]. In our study gefitinib was favorably accepted and had fewer systemic effects and it can be warranted that GST has a potential role in pretreated HNSCC.

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