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Review Article

Pharmacoeconomic Comparison of Various Palliative Cancer Chemotherapies in Head and Neck Cancers: India's Need

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ABSTRACT

Considering that India's middle class is not far above the International Poverty line and illness makes our population vulnerable to fall back into poverty. There is a pressing need to identify cost effective palliative chemotherapy medicines for the common man in India and apply the principles of pharmacoeconomics as an important priority in deciding the palliative chemotherapy medicines for the cancer patients. Pharmacoeconomics identifies and compares the costs and consequences of drug therapy to healthcare systems and society. This review article aims at compiling the current data available on the pharmacoeconomically cost effective palliative chemotherapy available for head and neck cancers and is meant to highlight important palliative chemotherapy medicines in head and neck cancers, comparing its cost and improvement in Quality of Life (QOL), TWIST (Time Without Symptoms or Toxicities) score/symptom control, Response Rate, survival advantage to overall guide the decisions of patient and their families in a ethically justified manner.

Keywords: Palliative chemotherapy, Pharmacoeconomics, Head cancer, Neck cancer, Cost effective

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INTRODUCTION

Cancer is a major cause of disastrous health expenditures, morbidity and mortality in both the developing and developed countries. World Bank reported, India to have the largest number of people (800 million; 30% of India's population) living below international poverty line. India's middle class is not far above the International Poverty line and illness makes our population vulnerable to fall back into poverty.

Annually, in India approximately 1 million people are newly diagnosed with cancer and over 7,00,000 die as a result of their malignancies (Krishnan S, *et al*., 2015). There is an urgent need for India and other countries for developing and applying the principles of pharmacoeconomics to cancer Chemotherapy medicines to prevent bankrupting the patient or the health care system. It becomes further important to address that when Chemotherapy is of palliative intent the patient and relatives must clearly understand the goals of care and the unrealistic hopes and expectations of the patients and relatives regarding prognosis must be addressed and explained well with the benefits and risks as there seems a difference in understanding of the doctors and the patients and their relatives when highly expensive palliative chemotherapy medicines are prescribed. It is therefore important to identify pharmacoeconomically valuable palliative chemotherapy for various cancers and prioritize them in the cancer care guidelines in Indian scenario. One of the reasons for patient drop outs from the radiotherapy or Chemotherapy treatment is cost constraints. Also as radiotherapy centers in our country are limited and far away from the reach of a patient living in a village it further adds to the indirect costs for the patients (stay and travel). There is a pressing need to identify cost effective palliative chemotherapy medicines for the common man in India and apply the principles of pharmacoeconomics as an important priority in deciding the palliative chemotherapy medicines for the cancer patients. Head and neck cancers account for more than 5,50,000 cases and 3,80,000 deaths annually worldwide and are the 6th most common cancer type. In India, head and neck cancers constitute alone third of the cancer burden (Ghantous Y and Elnaaj A, 2017).

Hence the need to review the data available on pharmacoeconomically valuable or cost effective palliative chemotherapy medicines available for various common cancers like head and Neck cancers in our country.

LITERTURE REVIEW

This review article aims at compiling the current data available on the pharmacoeconomic or cost effective palliative chemotherapy available for head and neck cancers and might serve as a basis for conducting further research in the same area. This review is not meant to exhaustively enumerate every palliative chemotherapeutic agent used in head and neck cancers, but rather is meant to highlight important palliative chemotherapy medicines and its pharmacoeconomic advantage comparing its cost and improvement in Quality of Life, TWIST score/symptom control, Response Rate, survival advantage. Search engines are Google, Pubmed, Pubmed central, and BMC.

Definitions

Few important terms used in the article are defined here:

Palliative chemotherapy: It is chemotherapy given in the non-curative setting to optimize symptom control, improve Quality of Life, and sometimes to improve survival (Roeland EJ and Leblanc TW, 2016).

Pharmacoeconomics: Pharmacoeconomics identifies, measures, and compares the costs and consequences of drug therapy to healthcare systems and society (Dipiro JT, *et al*., 2014).

The two fundamental components of pharmacoeconomic studies are measures of costs and measures of outcomes that are combined into a quantitative measure or ratio. It can be done using various methods like Cost-Minimization Analysis (CMA), Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), and Cost-Benefit Analysis (CBA). Authors of this article have made an attempt to compare the research studies of palliative chemotherapy in a tabular format using various parameters *viz*. improvement in symptom control, Quality of Life, Response Rates and Overall Survival advantage and cost of medicines used

for 6 months and not specifically conducted a CMA, CEA, CUA, CBA analysis as multiple parameters were involved.

Overall Survival (OS): It is broadly the duration between dates of treatment start (for the first palliative, systemic, non-trial treatment) and date of death as registered in the hospital record. It is defined as the time from random assignment to the date of death due to any cause, or to the date of censoring at the last time the subject was known to be alive in intention-to-treat populations (Patil V, *et al*., 2018).

Progression-Free Survival (PFS): Progression-Free Survival (PFS) is defined as the time from random assignment in a clinical trial to disease progression or death from any cause. It is broadly the time from treatment start to disease progression, defined as: (1) Clinical or radiological progression of recurrent tumor and/or distant metastases (2) start of new treatment (with the exception of treatment change due to toxicity) or (3) death, whichever occurred first. A second primary tumor was not classified as disease progression (Patil V, *et al*., 2018).

Response Rate (RR): Response Rate determinations reflect tumors that exhibit a complete regression or show a defined reduction for a specified time period. Stable tumors are excluded from Response Rate determinations (Pazdur R, 2000). Questions regarding the relationship between Response Rate and survival are increasingly complicated. With novel agents that do not exert their effect through tumor reduction, Response Rates may be of little value to accurately assess biologic activity and predict clinical benefit.

Clinical benefit: A regulatory end point used in traditional drug approval, has generally been characterized by an increase in patient survival, an unambiguous gold standard of efficacy, or by relieving or delaying the onset of disease-related symptoms. The demonstration of improving survival may be obscured by subsequent therapies after disease progression in randomized trials. Relief of tumor-related symptoms has been difficult to document in oncology trials because of traditionally restrictive eligibility criteria that allow only asymptomatic or early symptomatic patients into the trials (Pazdur R, 2000).

TWIST score (Time Without Symptoms or Toxicities): It was calculated by deducting the sum of time spent with complications/worsening of the baseline symptoms, and for treatment from the Overall Survival of the patients from the initial diagnosis of metastatic head and neck cancer (Patil V, *et al*., 2018).

Therefore an attempt has been made by authors to compare the cost of the palliative chemotherapy medicines available for various head and neck cancers with the benefit in symptom control, improvement in Quality of Life, better Response Rates, improved survival so as to help the health care policy makers to decide for best value for money of patients for palliative chemotherapy drugs.

Palliative chemotherapies in head and neck cancers

For palliation of patients with Recurrent and/or Metastatic Head and Neck Squamous Cell Cancer (R/M HNSCC), the major classes of commonly used cytotoxic chemotherapeutic agents are platinum agents (Cisplatin-(CIP), carboplatin), taxanes (paclitaxel, docetaxel), antimetabolic agents (Methotrexate (MXT), 5-Fluorouracil-(5-FU)), Methotrexate, cetuximab etc (Fury MG and Pfister DG, 2011). They can be used as monotherapy or in various combination regimens. The first-line treatment for incurable R/M HNSCC has been combination Chemotherapy with Cisplatin and 5-FU due to better Response Rates. Methotrexate (MXT) is another agent that is considered as an appropriate initial treatment for the majority of the patients (Sharma M, *et al*., 2014). A number of trials analyzed individually in 1980 concluded that Cisplatin as a single agent is not superior to Methotrexate in terms of response or median survival. The taxanes (paclitaxel, docitaxel) are certainly more difficult to administer and more costly. Taxanes may be the treatment of choice for patients whose renal dysfunction precludes the use of MTX or CIP (Colevas AD, 2006).

Unfortunately, it is unclear to what extent the use of these agents has brought about meaningful improvement in symptom control, Quality of Life and clinically relevant outcomes in these settings. Cisplatin has been associated with increased survival versus supportive care in only one small study (Price KA and Cohen EE, 2012). It is thought provoking that though Cisplatin based regimens did not demonstrate improved survival, offer better Quality of Life or better control of symptoms; this palliative chemotherapy regimen is preferred on the basis of Response Rate at the cost of greater toxicity for the patient and hence could compromise the Quality of Life of the patient further. Therefore a need for thorough discussion with the patients about the benefit they are expecting with the palliative chemotherapy and why was a particular palliative chemotherapy regimen chosen for that patient is very important? As most of the palliative chemotherapy regimens offered a comparable median survival advantage and studies comparing these Chemotherapy medicines for symptom control and Quality of Life is limited it becomes important to compare the direct and indirect costs involved in the overall palliative chemotherapy treatment decided for any patient. Further studies comparing various palliative chemotherapy medicines for symptom control, Quality of Life and median survival need to be done to actually do justice to the definition of palliative chemotherapy where priority is symptom control and Quality of Life and sometimes improve survival.

A study conducted recently demonstrated good palliation and improved progression free survival with Methotrexate, gefitinib, and combination arms, which is superior to 5-FU+Cisplatin arm and were better tolerated (Anuradha V, *et al*., 2013). Lately, gefitinib has been considered as an effective chemotherapeutic agent which it lacks any serious adverse reactions and has offered improved Quality of Life even in patients with poor performance status (Anuradha V, *et al*., 2013; Rao RR, *et al*., 2007).

Yet another study comparing gefitinib, Methotrexate and Methotrexate plus 5-FU revealed higher Quality of Life (QOL) of gefitinib at after 2 month and after 4 month as compared to MTX, however the mean Quality of Life was statistically same in all the groups. The median overall survival was not statistically different in all the groups (Kushwaha *VS*, *et al*., 2015).

When using Response Rates as the clinical trial end point for recurrent disease, Cisplatin-based combinations appeared to be superior to single agents, but at a cost of greater toxicity and without demonstrating improved survival or other indicators of clinical benefit.

Methotrexate is another single agent Chemotherapy that is preferred as a palliative chemotherapy agent for Squamous Cell Carcinoma of Head and Neck cancer patients. Recently gefitinib has demonstrated good palliation with a better Quality of Life for the patients in the initial months of treatment for SCCHN. However tablet gefitinib 250 mg (Glenmark Company) costs approximately Rs 2470 for 30 tablets is much more costlier than tablet Methotrexate 10 mg (Cipla Company) which costs approximately Rs 375 for 30 tablets.

Several Chemotherapy drugs which are active in R/M HNSCC most notably the platinum compounds, taxanes, Fluorouracil (5-FU), Methotrexate, gefitinib and cetuximab. Approximately 10%-25% of patients will respond to treatment with one of these drugs. The Response Rate is higher for combinations such as platinum plus a taxane, platinum plus 5-FU, a combination of the three, or one of more of these drugs plus cetuximab. Combination Chemotherapy has not been shown to prolong survival over single-agent therapy, with the exception of the addition of cetuximab to a platinum and 5-FU combination (Kushwaha *VS*, *et al*., 2015). The major development of the past decade in the first-line treatment of Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M SCCHN) was the introduction of cetuximab in combination with platinum plus 5-Fluorouracil Chemotherapy (CT), followed by maintenance cetuximab (the "EXTREME" regimen) (Argiris A, *et al*., 2017). Ce-

tuximab was the first targeted therapy approved in the first line for R/M SCCHN, conferring survival benefits in combination with platinum-based CT (Price KA and Cohen EE, 2012; Vermorken JB, *et al*., 2008; Bonner JA, *et al*., 2015; Taylor RJ, *et al*., 2015).

The survival improvement with EXTREME regimen (cetuximab+5-FU+Cisplatin) was significant from 7.4 months to 10.1 months with a cost of addition of cetuximab-six cycles for Rs 6 lakhs in comparison to the 5-FU+Cisplatin combination regimen which costs approximately Rs 9,000 for six cycles. It is prudent to discuss here that the patient and the family must be informed about both the survival advantage at increased costs. Inadequate sharing of expected benefit and cost involved may sometimes leave the patient and the family in huge debts for small improvement of survival advantage in months. One study also concluded that the EXTREME-regimen may not add much to the overall median survival and may be more toxic than expected when used in patients with R/M HNSCC outside clinical trials. 11 of 22 patients ended the treatment due to side effects. Three patients died within the first months due to side effects of the treatment. Two patients died of febrile neutropenia after the first cycle of treatment (Lynggaard CD, *et al*., 2015).

It also needs a consideration at this point that primary end point of many palliative chemotherapy studies is Overall Survival or Response Rates and a lot of times improvement in symptom control and Quality of Life of the patient is not included as an important evaluation parameter even when the definition of palliative chemotherapy states that it is the chemotherapy given in the non-curative setting to optimize symptom control, improve Quality of Life, and sometimes to improve survival (Roeland EJ and LeBlanc TW, 2016). A thorough re-consideration of further conducting palliative chemotherapy studies with the intention to offer better symptom control and improved Quality of Life as primary end points must be a high priority future need (Demargel M, 2017; Stoppler MC, 2018; Baile WF, *et al*., 2000).

Cost effectiveness of various Chemotherapy (CT) medicines for head and neck cancers

Methotrexate, Cisplatin+5-FU based regimens appear to be cost effective choices as compared to other anti-cancer Chemotherapy medicines for advanced head and neck cancers (Le X and Hanna EY, 2018). Even though the cetuximab based (EXTREME) regimen offers reduction in pain, improved Quality of Life and survival advantage of approximately 2-3 months it needs a thorough discussion with the patients about the actual cost and benefits of this regimen before the Chemotherapy regimen is decided so as to ensure that the patient and their relatives do not keep false hopes with this expensive cetuximab based Chemotherapy treatment (Jacobs C, *et al*., 1992; Glisson BS, 2002). Gefitinib appears to be a promising new drug for advanced head and neck cancer patients offering improved Quality of Life and TWIST scores and hence offering a good palliation, however cost is a limiting factor for the medicine for the low and middle income group in India (Zenda S, *et al*., 2007). It needs a mention to the patients that apart from the cetuximab based EXTREME regimen none of the Chemotherapy medicines offered a survival advantage in advanced head and neck cancers and this information needs a clear sharing with the patients and relatives (Mehra R, *et al*., 2008; Vermorken JB, *et al*., 2008).

It is suggested that the patients could be guided by standard set questionnaires about their queries to the oncologists on extent of disease, patient symptomatology, performance status, affordability, available logistic/social support and various palliative chemotherapy regimens available (Mesia R, *et al*., 2010). Considering the poor Oncologist and patient ratios in India, medical oncology trained palliative care professionals or medical officers could be appointed to assist the oncologists for counseling the patients on deciding the best possible palliative chemotherapy plan for the patient.

Please find below a proposed questionnaire for patients undergoing palliative chemotherapy for advanced head and neck cancers *(Table 1)*.

Table 1: Proposed questionnaire format for specific information needed

Questions to be asked by patients undergoing palliative chemotherapy (these questions are in addition to the general set of questions to be used to guide your patient about cancer chemotherapy)	
Q1	What is the goal of my palliative chemotherapy treatment?
Q2	What do you mean when you say palliative chemotherapy?
Q3	Will I get cured from this disease? The doctor/nurse must consider it might be a bad news for the patient and may be the first time this information is revealed and be prepared with the spikes format of breaking the bad news.
Q4	When will the effects of the treatment be evaluated?
Q5	How will you decide if the treatment is working?
Q6	What is the cost of palliative chemotherapy treatment for 6 months that I am receiving?
Q7	What advantages does this palliative chemotherapy plan give me in terms of survival advantage, Response Rates, symptom control and Quality of Life?
Q8	Is there any other cheaper alternative plan for palliative chemotherapy?
Q9	Why are we not choosing that?
Q10	Is there any better palliative chemotherapy plan? Cost is not an issue and if I want the best palliative chemotherapy available, what will be that?
Q11.	Considering my situation what advantages does this chosen palliative chemotherapy plan gives me in terms of survival advantage, Response Rates, symptom control and Quality of Life?
Q11	What are the alternatives if the palliative chemotherapy treatment is not effective or I choose not to take palliative chemotherapy?
Q12	Will I be offered support and cared by your team even if I choose not to continue with palliative chemotherapy? If not then is there any organization offering supportive and palliative care?

Given these premises, palliative and supportive care is of paramount importance along with the palliative chemotherapy treatment of head and neck cancers: It entails all the pharmacological interventions at an achievable cost aimed to prevent, manage, and mitigate the multi-factorial burden of symptoms that may occur as a consequence of the disease and/or its treatments and paramount importance needs to be given to symptom control and Quality of Life with palliative chemotherapy rather than Response Rates of tumor reminding us that we are treating the whole patient and not the disease.

DISCUSSION

As palliative chemotherapy states that it is the Chemotherapy given in the non-curative setting to optimize symptom control, improve Quality of Life, and sometimes to improve survival, therefore a discussion on palliative chemotherapy options available for head and neck cancers for offering good symptom control and Quality of Life at a reasonable cost needs to be done (Ham JC, *et al*., 2020).

The comparative studies of various palliative chemotherapy options for head and neck cancers on basis of improvement in symptom control, Quality of Life, Overall Survival, Response Rates and cost comparison reveal that gefitinib, Methotrexate and 5-FU+Cisplatin, are good options

for consideration in palliative chemotherapy for head and neck cancer patients. Combination of Methotrexate and gefitinib was inferior in terms of symptom control/TWIST scores and Quality of Life of patients; however Response Rates appeared higher as compared to gefitinib treatment alone. The decreasing order of TWIST score gefitinib (216 days), gefitinib+Methotrexate (185 days), Methotrexate (163 days) and 5-FU+Cisplatin (102 days) reveal that gefitinib alone offers good symptom control over other Chemotherapy medicines however a six monthly cost of treatment of gefitinib is approximately Rs 14,820 which might not be affordable by a patient from low socioeconomic strata in India and then weekly intramuscular Methotrexate injections might be a good option available for such patients which is around Rs 831 for 6 months. It will be good to open up discussions with the patients and allow patient autonomy for making such informed decisions on which medicine to choose for the patient for palliative chemotherapy promoting personalized and individualized pharmacotherapy. TWIST scores of 5-FU+Cisplatin were less than Methotrexate and might be considered inferior to Methotrexate in improving symptom control (Kirby AM, *et al*., 2006). For those who can afford cetuximab based-EXTREME regimen (cetuximab+5-FU+Cisplatin) which offered significant improvement in pain, problems with swallowing, speech and social eating and does not adversely affect the Quality of Life of patients. It has also shown significant survival advantage from 7.4 months to 10.1 months. However the six cycle treatment costs approximately Rs 6,35,937.6 which might be beyond the scope of an average Indian and needs to be discussed with the patient. No patient should be kept in dark and spends such a huge amount hoping of cure when studies have revealed survival benefit of months with the EXTREME regimen of cetuximab. Docetaxel based palliative chemotherapy offered a TWIST score of 61 days which was much below other palliative chemotherapy regimens for head and neck cancers and the cost of treatment for 6 cycles was approximately Rs 86,000 therefore docetaxel based regimens may not be a good option to consider for palliative chemotherapy (Tang X, *et al*., 2019). Tablet gefitinib and injection/tablets of Methotrexate gives the patient an added advantage that they may continue their palliative chemotherapies from the comfort of their homes and added costs of travel, hospitalization may be saved which has not been considered in the *Table 2*.

Table 2: Comparison of symptom control, quality of life, survival advantage, response rates and cost of various palliative chemotherapy regimens in head and neck cancers

S.no.	Palliative chemotherapy medicines	Symptom control/TWIST scores (days)	Quality of Life (QOL) percentage improvement from baseline	Survival advantage (median overall survival)	Response Rate (%) (RR)	Cost of medicines (in Rupees)
1.	Cisplatin	Symptom control/ TWIST score have not been found on search engines for Cisplatin alone.	No study individually assessing Cisplatin alone as palliative chemotherapy and the QOL could be found.	A 2.2% overall survival benefit between the chemo-radiotherapy group and the radiotherapy alone group was observed for every 10 mg increase in the cumulative Cisplatin dose. It is generally accepted that cumulative dose of Cisplatin greater or equal to 200 mg/m^2 confers a survival benefit.	17%	Cost/50 ml: 1 mg/ml-50 ml-Rs 316 (Zydus) Dose: 50-100 mg/m^2 for every 3weeks Cost for 6 cycles: Rs 7204.8 for 100 mg/m^2 dose.
2.	Taxanes-docetaxel	TWIST score: 61 days	No study individually assessing docetaxel alone for palliative chemotherapy and the QOL could be found.	No study individually assessing docetaxel alone as palliative chemotherapy and overall survival could be found.	10%-45%	Cost/3 ml: Rs 14,999.00 for 120 mg/3 mL (Wockhardt Ltd.) Dose: 60 mg/m^2 was administered every 3-4 weeks Cost for 6 cycles: Rs 85,494.3
3.	Cisplatin+ 5-Fluro-uracil	TWIST score: 102 days(14)	No study individually assessing Cisplatin+5FU alone for palliative chemotherapy and the QOL could be found.	No significant difference in median survival as compared to single agent alone.	Overall response rate was superior in combination (32%) to Cisplatin (17%) or 5FU (13%) alone.	Cisplatin (100 mg/m^2) details already provided in S no:1 Cost/10 ml 5-FU 500 mg/10 ml Rs 19(Cadila) Dose: (1000 mg/m^2 × 4) every 3 weeks for 6 cycles. Cost for 6 cycles: Rs 8937.6

4.	Cetuximab	TWIST analysis/ symptom control could be found	No study individually assessing cetuximab alone as palliative chemotherapy and QOL could be found.	A phase III multicenter Randomized Trial (RT) 424 patients between definitive RT and RT with cetuximab. There was an improvement in median survival from 29.3 to 49 months (p=0.03).	10%-13%	Cost of 500 mg cetuximab- approx.1 lakh per 500 mg-(Merck company) Dose: 400 mg/m^2 followed by subsequent weekly 1-hour infusions of 250 mg/m^2. Cost for 6 cycles: Total: 6 lakh and 27 thousand for 6 cycles.
5.	Cisplatin+5FU+ cetuximab (maintenance) (EXTREME regimen)	TWIST scoring not available but studies report significant improvement in pain, problems with swallowing, speech and social eating.	Adding cetuximab does not adversely affecting QOL. At cycle 3, statistically significant differences in favor of the cetuximab arm for pain and problems with swallowing, speech, and social eating were observed.	Significant improvement in overall survival from 7.4 months to 10.1 months.	Overall response rates between 36% and 44%	Cost of Cisplatin+5-FU and cetuximab discussed in S no:1 and 4 Dose: Cisplatin: Patients received a maximum of six cycles of Cisplatin (at a dose of 100 mg/m^2 5-FU (at a dose of 1000 mg/m^2 per day for 4 days) every three weeks followed by cetuximab maintenance with 250 mg/m^2 every week until disease progression. Cetuximab (at a dose of 400 mg/m^2 initially, as a 2-hour intravenous (loading dose) infusion, then 250 mg/m^2, as a 1-hour intravenous infusion per week) on day 1 and cost for 6 cycles cetuximab six cycles (627000Rs)+Cisplatin and 5-FU 6 cycles (8937.6) Total: Rs 627000+8937.6=Rs 6,35,937.6
6.	Methotrexate	TWIST score: 163days	45%	5.3 months for Methotrexate as compared to gefitinib-6.1 months, Cisplatin+5-FU-3.9 months and gefitinib+Methotrexate-9.2 months.	5%-10%	Cost of 2 ml 50 mg/ml-2 ml: Rs 69.25 (Zydus) Dose: Weekly intramuscular dose for 6 months Cost for 6 months treatment: Rs 831
7.	Gefitinib	216 days	85%	6.1 months	0%-19%	Cost of 30 tablets of 250 mg. (glenmark) Rs 2470 Dose: 250 mg od Cost of 6month treatment: Rs 14,820.
8.	Gefitinib+-Methotrexate	185 days	65%	9.2 months	63%	Cost discussed in S no. 6 and 7 Dose: Gefitinib was initially administered orally in a dose of 250 mg once daily calculated for 6 months Methotrexate was given as 50 mg intramuscular weekly(Rs 69.25) Cost of 6 months treatment: Rs 14820 (Gefitinib)+ Rs 831 (Methotrexate)=Rs 15,651
Note: Doses have been calculated on the basis of keeping a mean surface area of an average healthy man (1.9 m^2)						

There seems an overall need to open up discussions with the patient and family member to plan and individualize the pharmacoeconomically cost effective palliative chemotherapy plan in head and neck cancers.

CONCLUSION

The end point that will be achievable should be clearly stated right from the beginning and the families of the patients must be appropriately guided and prepared and be assured of support in all situations. Oncologists might be concerned about the huge patient load and paucity of time to open up such discussions. Therefore the authors suggest that based on individualized hospital settings a proper plan of training/appointing junior doctors trained in palliative care may be utilized for such discussions.

LIMITATIONS

The limitations of this review are that very few studies have incorporated symptom control and Quality of Life as an important evaluation parameter thereby indicating need of more studies where symptoms control and Quality of Life is given importance in palliative chemotherapy settings needs consideration. Due to these reasons a systematic review cannot be planned until we have more evidence on effect of the palliative chemotherapy medicines in head and neck cancers on symptom control and Quality of Life as primary objectives in further studies.

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