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REVIEW ARTICLE

Systemic Therapy in Head and Neck Cancer: Changing Paradigm

Samit Purohit · Rohan Bhise · D. Lokanatha · K. Govindbabu

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Abstract Head and neck cancers comprise a heterogenous group of cancers that require a multidisciplinary approach. Last few decades have seen an increasing role of chemotherapy with intent of treatment shifting from palliation to cure. We performed a thorough search online and offline for all relevant articles of chemotherapy in head and neck cancer. Cancers of nasopharynx and salivary glands were excluded.

Keywords Chemtherapy in head and neck cancer · HPV · PET-CT · MACH-NC · Chemoevolution in head and neck cancer

Introduction

Cancers of head and neck comprise a heterogenous group of malignancies extending from lips to the cervical esophagus with squamous cell cancer (SCC), representing the most prevalent histology. Head and neck cancers are among the ten most common cancers globally. In India, they account for one fourth of male cancers and one tenth of female cancers. The incidence has been gradually increasing over the last three decades (accounting for 30 % of all cancers). Tobacco and alcohol are among the common etiologic factors. Human papilloma virus is now a well known risk factor particularly for oropharyngeal cancers. Traditionally surgery, radiation or both have been the standard of care for these patients. Despite technical expertise in surgery and radiotherapy the survival rates remain unchanged. Local therapy with surgery or radiotherapy has achieved a cure rates of 80 % in stage I and 60 % in stage II disease. But most of the patients present in advance stages ie stage III & IV, their 5 year survival rates remain as low as 40 % and 20 % respectively. It is in this group that an emerging role of chemotherapy is being defined. Prospective and retrospective analysis of clinical trials have demonstrated a better outcome in HPV associated cancers as compared to HPV negative cancers (Table 1) and there is a growing consensus that HPV testing should be included as a baseline risk stratification specially for oropharyngeal cancers and carcinoma of unknown primary.

Last three decades have seen a paradigm change in the role of chemotherapy in head and neck squamous cell cancer (HNSCC). Prior to 1990's,the role of chemotherapy was limited to palliation of symptoms in advanced disease but now the objectives of chemotherapy in this field are dramatically changing.

Recurrent and Metastatic Disease

The role of chemotherapy in recurrent and metastatic setting is limited to the palliation of symptoms. In the latter half of the last century a variety of drugs either alone or in combination were tried with variable responses. These responses were of brief duration without any benefit in overall survival.

S. Purohit · R. Bhise · D. Lokanatha · K. Govindbabu
Department of Medical Oncology,
KMIO, Bangalore, India

R. Bhise
e-mail: rohanbhise30@gmail.com

D. Lokanatha
e-mail: drloku@gmail.com

K. Govindbabu
e-mail: kgblaugh@gmail.com

S. Purohit (✉)
Kidwai Memorial Institute of Oncology,
PG Hostel Room No. 202, Dr M.H Marigowda Road,
Bangalore 560029, India
e-mail: samitmedonc@gmail.com

Table 1 Impact of HPV on outcome in head and neck cancer

Study	Patients tested	Therapeutic regimens	HPV+/tested (%HPV+)	Result- survival (%)	HPV+/HPV−
RTOG 01-29 [1]	323/433 (75 %)	CRT versus RT	206/323 (65)	2-year OS	88 versus 66
				2-year PFS	72 versus 50
HeadStart, international [2]	195/465 (42 %)	CRT versus CRT	54/195 (28)	2-year OS	94 versus 77
				2-year PFS	NA
TAX 324 [3]	111/264 (42 %)	ST versus ST	56/111 (50)	5-year OS	82 versus 35
				5-year PFS	78 versus 28

OS overall survival; *PFS* progression-free survival; *HPV* human papillomavirus; *RTOG* Radiation Therapy Oncology Group; *CRT* chemo-radiotherapy; *RT* radiotherapy; *ST* sequential therapy; *NA* not available

Single Agents

Earliest agents to be tried were the platinum analogs mainly cisplatin. They belong to the alkylating class of drugs that act by forming covalent bonds with DNA. As a single agent in a total dose ranging from 80 to 120 mg/m2, every 3 to 4 weekly, cumulative responses of 13–40 % were seen. Tumor responses were rapid, often within a week of starting treatment. Peripheral neuropathy and ototoxicity were the dose limiting adverse effects (cumulative dose of more than 400 mg).In view of its toxicity, the other platin analog carboplatin was tried but the responses were as low as 26 %. Subsequently in 80's and 90' a couple of other agents were tried including methotrexate, 5-Flurouracil, bleomycin, ifosfamide with overall responses varying from 20 to 40 % (Table 2). In 1990's taxanes were introduced, these agents act by promoting microtubular assembly, cell cycle arrest and apoptosis in G2M phase of cell cycle. Paclitaxel and docetaxel tried in various phase II trials produced a response of 20–40 %. Other agents that are less well studied include adriamycin, vinblastine, irinotecan, cyclophosphamide, hydroxyurea and gemcitabine.

Combination Chemotherapy

Combination chemotherapy in recurrent and metastatic settings is used with a goal of achieving higher and more durable response rates. Several studies comparing single agent with a combination chemotherapy have shown superior responses with latter. In a phase III trial by Jacob's et al. cisplatin alone was compared with cisplatin, methotrexate and leucovorin. Responses were 18 % (CR-8 %) and 33 % (CR-15 %) respectively [16]. Other trials comparing single agent methotrexate with a combination of cisplatin, bleomycin, vinblastine or vincristine showed a higher responses with combination arm [17, 18]. Three large multicentre trials reported a statistically significant improvement in overall response rates for cisplatin and 5 Fu combination compared to single agent(32 % and complete response of 6 %) [19–21]. Browman and Cronin performed a metaanalysis of 15 trials where single agent was

Table 2 Single agents responses in metastatic and advanced head and neck cancer

Agent	Author	Phase	Dose	Overall response rates
Cisplatin	Campbell et al. [4]	III	100 mg/m2,4 weekly	40 %
	Morton et al. [5]	III	100 mg/m2, 4 weekly	13.3 %
Carboplatin	Eisenberger et al. [6]	I	60–80 mg/m2 daily (day 1–5), q 4–5 weekly	25 %
Methotrexate	Eisenberger et al. [7]	III	40 mg/m2/week	25 %
	Schornagel et al. [8]	III	40 mg/m2/week	16 %
5-Fu	Tapazoglou et al. [9]	II	1 g/m2, c.i.v.i. (Day 1–4), 3 weekly	72 %
Bleomycin	Morton et al. [5]	III	15 mg/m2 (Day 1–5)	13.6 %
Ifosfamide	Buesa et al. [10]	II	5–6.25 g/m2/day (Day 1–5), 4 weekly	28 %
	Cervellino et al. [11]	II	3.5 g/m2/day	42.7 %
Docetaxel	Couteau et al. [12]	II	100 mg/m2, 3 weekly	21 %
	Dreyfuss et al. [13]	II	100 mg/m2, 3 weekly	42 %
Paclitaxel	Gebbia et al. [14]	II	175 mg/m2 (3 h), 3 weekly	20 %
	Smith et al. [15]	II	250 mg/m2 (24 h), 3 weekly	35 %

Less well studies agents include Adriamycin, Vinblastine, Irinotecan, Cyclophosphamide, gemcitabine and hydroxyurea

Single agents responses vary from 15 to 30 %

Median duration of response is brief ie 2–3 months.

Overall survival not affected (average 6 months)

compared to combination chemotherapy. They concluded that combination of agents produced a statistically significant improvement in responses. The combination of cisplatin and 5 Fu seemed to be the most widely used. Addition of other agents to this combination resulted in higher toxicities without any improvement in complete responses or survival [22]. The combination of cisplatin (100 mg/m2 on day 1) and 5 Fu (750 mg/m2 day 1–5) in a patient of good performance status remains the most widely used regime (Table 3).

With the impressive single agent activity of taxanes in earlier studies, an intergroup trial was initiated by ECOG group that compared paclitaxel (175 mg/m2 over 3 h) and cisplatin (75 mg/m2) with cisplatin and 5 Fu. No difference in response rates, overall survival or quality of life was seen [23]. Docetaxel (100 mg/m2) in combination with cisplatin (75 mg/m2 every 3 weekly) has been tried in EORTC trial in taxane naïve patients. Overall responses were 53.7 % (complete responses of 15 %). Median duration of responses were 18 months. Major adverse events noted were hematologic mainly anemia (98 %) and leucopenia (79 %) [24]. Unfortunately all the above mentioned trials and many others failed to demonstrate any survival benefit. Another major critical drawback of earlier studies was the consideration of responses rather than survival as primary end point. Moreover they failed to determine the impact of treatment on the quality of life.

Chemotherapy in Primary Management of Head and Neck Cancer

Earlier, small pilot studies with cisplatin had shown rapid tumor regression in a major percentage of newly diagnosed cases. Extrapolating this information led to the incorporation of chemotherapy into the combined modality treatment with a curative intent. There are several ways by which chemotherapy can be used with a locoregional modality of treatment, 1) Neoadjuvant (Induction) chemotherapy, 2) Concurrent chemoradiotherapy and 3) Adjuvant chemotherapy (with radiation).

1) Neoadjuvant (Induction) chemotherapy

The rationale behind the use of induction chemotherapy is that reduction in tumor size may improve local control achievable with subsequent definite treatment. This is feasible due to the better vascularization of tissues prior to any local form of treatment. Induction chemotherapy also takes care of micrometastasis leading to improved survival and it may serve as a surrogate marker for the efficacy of radiotherapy later. Prior to 1990's i.e the pre-taxane era, various multidrug combination were tried that included cisplatin, 5Fu, bleomycin, methotrexate with vinca alkaloids [25–27]. Overall response rates of 70 % and complete responses of 20–30 % were seen. In 1980's, various trials combining cisplatin with 5 Fu were done and a overall response of 80 % with complete response of 40–50 % were achieved but without any survival benefit. Efforts to intensify the therapy by adding leucovorin (a biological response modifier) and interferon–alpha was associated with higher responses at the cost of severe gastrointestinal and hematological toxicities. Another randomized trial comparing cisplatin and 5 Fu with carboplatin and 5 Fu demonstrated the superiority of the former in terms of responses (92 % vs 76 %), disease free survival (47 % vs 24 %) and 5 year survival (45 % vs 24 %)

Table 3 Outcomes with combination chemotherapy in metastatic head and neck Ca

Study	Agents	Response rates	Median overall survival in months (m)
Jacobs et al. [16]	CDDP	18 %	8 m
	Vs		
	CDDP/MTX/Leucovorin	33 %	8 m
Drelichman et al. [17]	MTX	16 %	6 m
	Vs		
	CDDP/Bleo/Oncovin	24 %	6 m
Williams et al. [18].	MTX	16 %	7.7 m
	Vs		
	CDDP/Bleo/Vinblastine	24 %	7.2 m
Jacobs et al. [19]	5-Fu	13 %	6.1 m
	CDDP	17 %	5.0 m
	5-Fu/CDDP	32 %	5.5 m
Clavel et al. [21]	5- Fu/CDDP	31 %	6.1 m
	Vs		
	CDDP/Oncovin/Bleo/MTX(CABO)	34 %	8.2 m

CDDP cisplatin, *MTX* methotrexate, *Bleo(B)* bleomycin, *Oncovin(O)* vincristine, *5-Fu* 5fluorouracil

[28]. In contrast a randomized trial limited to patients with locoregionally advanced oropharyngeal cancer reported by Domenge et al., showed that induction chemotherapy with cisplatin and 5-fluorouracil significantly improved survival (P=0.03) compared to locoregional treatment alone (i.e., surgery plus radiation or radiation alone) [29]. Even in the absence of survival benefit in majority of studies, there seemed to be a correlation between response to the chemotherapy and subsequent response to radiation, which provided a basis for subsequent organ preservation studies.

Induction Chemotherapy for Organ Preservation

Traditionally, surgery was the treatment of choice for advanced cancers of larynx and hypopharynx. However with the impressive results to neoadjuvant chemotherapy and subsequent favourable responses to radiotherapy, studies were done that demonstrated that an optimum local control could be achieved without compromising the functional outcome, cosmesis and survival (Table 4). In a landmark study by the veterans administration cooperative study program (VACSP), 332 patients with stage III or IV resectable laryngeal cancer were randomized to either induction chemotherapy (3 cycles of cisplatin and 5 Fu) followed by radiotherapy or laryngectomy depending on the responses. The other arm underwent laryngectomy followed by radiotherapy. Induction chemotherapy with radiation resulted in a response rates of 80 %. Larynx was preserved in 66 % of patients and overall survival was comparable in both arms at the end of 3 years (53 % vs 56 %, p = insignificant). In a subgroup analysis, T4 lesions were associated with increased risk of failure after induction chemotherapy [30]. In a subsequent study by the EORTC head and neck cooperative group, 194 patients with cancer of pyriform sinus (80 %) and epilarynx (22 %) belonging to stage II, III and IV were randomized into two arms like the veterans affair laryngeal study group. Both arms had similar local (83 % vs 88 %) and regional control (77 % vs 81 %) (p = insignificant). Five year overall survival was comparable in both groups [31]. Both these laryngeal preservation trials established induction chemotherapy followed by radiation as standard of care for advanced laryngeal cancer. However this outlook changed with another landmark study by Forastiere and colleagues (RTOG 91-11), where 547 patients of stage III and IV resectable laryngeal cancers were randomised into three arms. Arm A received induction chemotherapy (three cycles cisplatin and 5 Fu) followed by radiation. Arm B received concurrent chemoradiotherapy (cisplatin, 100 mg/m2 q3weekly). Arm C patients received only radiation (70 Gy/7 weeks). Concomitant chemoradiotherapy resulted in improved 2 year laryngectomy free survival as compared to the other two arms. At the end of 5 years, the rate of laryngeal preservation was 70 %, 88 % and 65 % in Arm A, B and C respectively. Progression free survival was 38 %, 39 % and 27 % respectively (Both P value significant). Overall survival was similar in all the three arms [32].

Patients treated with induction chemotherapy continue to have a high rate of locoregional failure, whereas chemoradiotherapy has reduced locoregional treatment failure with no improvement in control of distant disease. This led to the development of sequential therapy approaches, combining induction chemotherapy, chemoradiotherapy, and surgery. In a phase III study (TAX 324), 539 treatment naive patients with HNSCC stage III/IV disease were randomized into two arms. First arm received docetaxel (75 mg/m^2 IV), cisplatin (100 mg/m^2 IV), 5-FU (1,000 mg/m^2/day IV) daily for 4 days every 3 weeks for 3 cycles. Arm two received cisplatin (100 mg/m^2 IV) and5-FU (1,000 mg/m^2/day CI) daily for 5 days, every 3 weeks for 3 cycles. Later both arms received concurrent chemoradiation (carboplatin, AUC 1.5, weekly and daily radiotherapy, 5 days/week, followed by surgery as needed. Primary endpoint was overall survival and secondary endpoint was progression free survival and toxicity. Overall response trend favored TPF vs. PF. (72 %

Table 4 Laryngeal preservation trials

Trial (year)	No. of patients (n)	Stage	Design (arms)	Result
VACSP, 1991	332	III & IV Laryngeal Ca	Arm A: Surgery f/b CT Arm B: CT f/b RT	3 year overall survival (53 % vs 56 %) both arms. Larynx preservation in 66 %
EORTC, 1996	194	II,III,IV	Arm A: Surgery f/b CT	5 year overall survival equal in both arms
		Laryngeal Ca	Arm B: CT f/b RT	Larynx preservation 33 % at 5 year
RTOG (91-11) (2001)	547	III, IV	Arm A: Conc.CT + RT	5 year overall survival equal in 3 arms
		Laryngeal Ca	Arm B: CT f/b RT	Larynx preservation in Arm A: 70 %
			Arm C: RT only	Arm B: 88 %
				Arm C: 65 % (P: sig)

VACSP veterans administration cooperative study program, *EORTC* European organisation for research and treatment of cancer, *RTOG* radiation therapy oncology group

vs. 64 %; P=.07).At the end of 3 years overall survival was 62 % in TPF and 48 % in PF arm. Even though TPF arm had a higher incidence of hematological toxicities. G.I toxicity was similar in both the arms and there were no toxicity related deaths [33].

2) Concomitant Chemoradiotherapy

Combined use of chemotherapy and radiotherapy has been studied due to poor local control achieved with surgery or radiotherapy alone. In general chemotherapy can be combined with radiotherapy in three ways. First as a single agent or combination chemotherapy with continuous radiotherapy, second is combination chemotherapy with split course radiotherapy, often with altered fractionation and lastly chemotherapy alternating with radiotherapy. First two approaches are commonly used in clinical practice. A review of literature on trials comparing concurrent chemoradiotherapy with radiotherapy alone, favours the former. To date the largest meta-analysis done in head and neck cancer ie the MACH-NC analysis clearly establishes the benefit of concurrent chemoradiotherapy in terms of overall survival(p value significant) [34]. Conclusions of the metaanalysis are summarized in Table 5. Platinums as a single agent have shown a positive impact when combined with radiation of which cisplatin is the predominant one studied. The combination of platinum plus 5 Fu offers no additional advantage over platinum alone. Largest benefit with addition of chemotherapy in concurrent setting was seen in cancers of larynx and oropharynx. The current NCCN guidelines recommend concurrent cisplatin with radiotherapy as a preferred choice. Concurrent chemotherapy is associated with significant toxicity and benefits of therapy should outweigh the risks involved.

3) Adjuvant Chemoradiotherapy

Chemotherapy as an adjunct to locoregional treatment seems to be a logical option theoretically but studies have failed to demonstrate a significant survival advantage. Patients with advance disease are at high risk for locoregional (40–60 %) or distant failures (20–30 %). Two randomized studies demonstrated the benefit of addition of postoperative chemoradiotherapy in the poor risk setting. The RTOG-9501 [35] and EORTC 22931 [36], randomized patients with poor risk features to either postoperative radiotherapy alone or radiotherapy with three cycles of concurrent cisplatin at 100 mg/m2 every 3 weekly. RTOG constituted the presence of two or more positive lymph nodes, positive margins and extracapsular extension as high risk factors while EORTC defined positive margins, extracapsular extension, pT3 and T4 with any N, N2 or N3 disease, level IV nodes, stage IV disease in oral cavity and oropharynx, perineural invasion or vascular invasion as high risk features. Both studies demonstrated a significant improvement in locoregional control and disease free survival. Overall survival was significantly improved in EORTC study. A subsequent analysis of both these studies revealed that extracapsular extension and positive margins benefited most from the combined modality treatment (conc CT + RT). Chemotherapy may be added to RT in cases with positive margin, pT3 and T4 with any N, N2 or N3 disease, level IV nodes, stage IV disease in oral cavity and oropharynx, perineural invasion or vascular invasion. Cases with two or more positive lymph nodes involvement without extracapsular invasion did equally well with radiotherapy only. Data about the use of chemotherapy alone in adjuvant setting is limited and at present there is no role of adjuvant chemotherapy alone in routine care of patients.

Supportive Care

Most patients with head and neck cancers lose weight as a result of their disease or treatment related toxicities. Nutritional management is very important to improve outcomes and minimize toxicities and thus all patients should receive

Table 5 Metaanalysis of chemotherapy in head and neck cancer (MACH-NC). 2011, update

- 87 randomized trials, between 1965 and 2000. (Previous update in 2000: 63 trials,10,000 patients)
- Over 16,192 patients analysed.
- Patients were divided into four categories according to tumour location ie oral cavity, oropharynx, hypopharynx and larynx. The hazard ratios of death or relapse were calculated with respect to type, timing of chemotherapy and tumor locations.
- With a median follow-up of 5.6 years, the benefit of the addition is consistent in all tumour locations, with hazard ratios between 0.87 and 0.88 (p-value of interaction=0.99). Chemotherapy benefit was higher for concomitant administration for all tumour locations, but the interaction test between chemotherapy timing and treatment effect was only significant for oropharyngeal (p<0.0001) and laryngeal tumours (p=0.05), and not for oral cavity and hypopharyngeal tumours.
- The 5-year absolute benefits associated with the concomitant chemotherapy are 8.9 %, 8.1 %, 5.4 % and 4 % for oral cavity, oropharynx, larynx and hypopharynx tumours, respectively.

Neoadjuvant trials (with taxanes) were not included in this metaanalysis

nutritional counselling from a trained dietician. Pre and post treatment functional assessment should be done with the help of subjective and objective assessment tools. Nutritional interventions like nasogastric tube, percutaneous endoscopic gastostomy (PEG) tube or intravenous nutritional support may be required especially for patients with poor performance status where radiotherapy is contemplated.

Targeted Therapeutics and Novel Agents

Last two decades have seen a better understanding of the molecular mechanisms underlying HNSCC and advances in molecular biology have led to the development of newer targeted agents. These include monoclonal antibodies and small tyrosine kinase inhibitors (TKI's). While monoclonal antibodies have an extracellular domain activity due to their large size, TKI's act intracellularly. Cetuximab, an immunoglobulin-G1 chimeric monoclonal antibody directed against EGFR, was the first molecularly targeted agent to be used HNSCC. Bonner et.al compared RT with cetuximab against RT alone (standard doses) in locally advanced HNSCC. The median duration of locoregional control was 24 months in RT with cetuximab versus 15 months in RT alone arm, Median survival was 49 months in combination as compared to 29 months in RT alone [37]. Cetuximab in combination with chemotherapy (cisplatin) has been tried in metastatic and recurrent settings demonstrating a responses of 6–20 % in previously treated cases without any improvement in survival [38]. In an ECOG trial, among 123 chemonaive patients cetuximab with cisplatin produced a response of 26 % with a PFS and OS of 4.2 months and 9.2 months respectively(p value insignificant) [39]. In another trial "EXTREME", 442 patients were randomized into two arms with platins and 5 fu with or without cetuximab for six cycles. Maintenance cetuximab was given in investigational arm. Improved PFS(5.6 m vs 3.3 m) and OS(10.1 m vs 7.4 m) was seen in the triplet arm at the cost of higher toxicity, although no deaths were reported due to cetuximab [40]. Another recombinant humanized monoclonal antibody (h-R3mAB), Nimotuzumab (Phase IIb) has shown some impressive results. Out of 110 patients screened, 92 patients with (stage III or IVa), inoperable SCCHN were randomized in 1:1 ratio in two groups; group A received [RT Vs RT + h-R3mAb] and group B received [CRT vs. CRT + h-R3mAb]. Treatment given included radiotherapy in total dose 60–66 Gy, h-R3mAb 200 mg by I.V infusion over 60 min/week for 6 weeks and in group B, chemotherapy CDDP 50 mg/week for 6 weeks. Seventy-six patients were evaluable for response ie 36 in group A and 40 in groupB. Locoregional response was 100 % in CRT + h-R3mAb vs. 70 % in CRT and 76 % in RT + h-R3mAb vs. 37 % in RT. At a median follow up of 48 months, overall survival rate in intention to treat(ITT) group was 47 % in (CRT + h-R3mAb) vs. 21 % (CRT) (p=0.01) and 34 % (RT + h-R3mAb) vs. 13 % (RT)(NS), median overall survival was not reached (NR) for (CRT + h-R3mAb) vs. 21.9 months (CRT)(HR-0.35, P-0.01) and 14.3 months (RT + h-R3mAb) vs. 12.7 months (RT)(HR-0.74, P-0.42). Adding h-R3mAb to chemoradiation resulted in significant reduction in risk of death by 65 % (HR 0.35, p-0.01). The concurrent use of h-R3mAb with RT/CRT seems to be safe and efficacious [41]. Other drugs like antiangiogenesis agents seem to be an interesting option however their development has been quite cautious due to earlier reported toxicities of bleeding and thrombosis. A multicentre phase II trial enrolled 40 patients with recurrent or metastatic head and neck cancer. Patients were treated with bevacizumab and pemetrexed given three weekly with folic acid and vitamin B12 supplementation. The median TTP was 5 months, and the median overall survival (OS) was 11.3 months. In 37 evaluable patients, the overall response rate was 30 %, including a complete response rate of 5 %, and the disease control rate was 86 % [42]. Among the small molecule tyrosine kinase inhibitors (TKI's), gefitinib and erlotinib have failed to demonstrate any efficacy in recurrent and metastatic settings. Future research aims at identifying certain genes and the use of cancer gene therapy. One such example is the P53 tumor suppressor gene that is mutated in patients who are long term smokers, could serve as a potential target. Other potential targets are IGF-R inhibitors and cyclin-D1 inhibitors that are still in early phase trials.

Chemoprevention

Individuals with early stage head and neck cancer after a definite treatment are at high risk for developing a second primary ie "field cancerization" due to the carcinogenic effects of tobacco on the epithelial surface of the aerodigestive tract. The risk of second primary is 3 to 4 % per year. Chemoprevention is the use of pharmacologic agents to reverse any premalignant condition even though it does not protect against recurrence from the index cancer. Agents tried include retinoids, carotenoids, n-acetylcysteine and cox-2 inhibitors. Retinoids in a few randomized placebo control trial resulted in reversal of dysplastic leukoplakic lesions and reduction in development of second tumors (31 % vs 14 %) at the end of 54 months [43]. However due to the toxicities (dry mouth, skin desquamation, hypertriglyceridemia), the

uncertainty of optimal dosing and duration, their use in current clinical practice is not recommended.

Emerging Role of PET-CT

The role of fused modality [F]-2-fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) in diagnosing and accurately staging patients with primary, metastatic, and recurrent head and neck cancer is evolving, and the clinical implications need to be further defined. A few retrospective studies have been performed, but adequate sample sizes are lacking. In a retrospective study by Fleming et al. in 268 patients, PET/CT was true-positive in 82.9 % and false-positivity was seen in 12.2 % patients. In 67 patients who underwent neck dissection, PET/CT had a positive predictive value (PPV) of 92.7 %. The accuracy was 89.7 % in 20 patients who had bilateral neck dissections. Treatment was altered in 30.9 % of previously untreated patients [44]. Current guidelines recommend the use of PET-CT in stage III and IV disease. A PET-CT may also be used for post treatment evaluation especially post radiation or chemoradiation. The ideal time is after 12 weeks to reduce false positivity. In a patient with clinically negative neck, PET-CT is 90 % accurate.

Summary

Much progress has been made regarding the role of chemotherapy in SCCHN with focus shifting from palliative to curative intent. The ongoing clinical studies continue to redefine the same. Current guidelines suggest the use of single modality treatment either surgery or radiotherapy in early stage HNSCC depending on the site. (oral cavity, paranasal sinuses, oropharynx, hypopharynx and larynx) ie stage I and II (N0). Postoperatively RT (with or without CT) may be added depending on the high risk features. In patients with resectable locally advanced head and neck cancers of oral cavity and paranasal sinuses, surgery followed by adjuvant therapy (RT + CT) is advocated. In resectable locally advanced cancers of larynx, hypopharynx and oropharynx, the options include chemoradiotherapy (Level 1 for larynx and oropharynx: MACH-NC), induction chemotherapy followed radiation (Level 1 for hypopharynx: EORTC). In unresectable subsets neoadjuvant chemotherapy (TPF) seems to be an interesting option with some survival benefit as shown in TAX-324 trial. Prognosis of metastatic and recurrent lesions remain poor and use of chemotherapy (single agent vs combination) should be tailored based on the performance status and immediate need of response. Interesting advances in the form of newer biotherapies (cetuximab) have shown some improved survival both in advanced and metastatic settings. Future research aims at isolating target receptors IGF-R (Insulin like growth factor receptor inhibitor) and cell cycle inhibitors (cyclin D1).

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