Selected Summary

Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer (THE TAX 324 trial)

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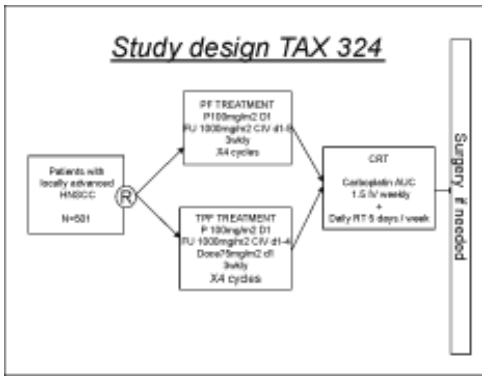
New England Journal of Medicine; October 25 2007;357(17):1695-704

Squamous cell carcinomas of the head and neck (SCCHN) account for about 5% of all cancers in the West.[1] In the India, they form around 20% of all cancers.[2] 60-70% present as locally advanced (stage III/IV) cancers.[3] Chemoradiotherapy (radiotherapy plus concurrent chemotherapy or CRT) is the standard of care for patients with locally advanced squamous-cell carcinoma of the head and neck and affords improved survival as well as organ preservation. However, the survival in the poorest risk groups remains dismal. Induction chemotherapy is an option which may have a role in these patients.[4,5] Currently, a combination of Cisplatin and Fluorouracil is the most popular regimen for induction chemotherapy. This regimen has a modest 5% survival benefit at 5 years.[6] Recent phase II studies have shown very high response rates with the use of triplet regimes by adding taxanes to the existing combination of cisplatin fluorouracil (PF).[7,8] It is hoped that these regimes would prove beneficial for this difficult to treat patient group.

This study, termed the TAX 324 trial[9] is a phase III randomized open label, Multi center trial conducted at centers in the US, Russia and UK. The existing standard regime of PF (cisplatin and 5 FU) was compared against a combination of Docetaxel + PF as induction chemotherapy in cases of locally advanced (stage III or IV) SCCHN. Both the arms were scheduled to receive concurrent chemoradiotherapy (CRT) subsequent to 4 cycles of induction chemotherapy. (Figure 1-study design).



The subjects included included histologically confirmed cases of locally advanced SCCHN with primary in the larynx, hypopharynx, oral cavity or oropharynx. They were in good general condition (Performance status 0-1), were previously untreated and had good organ function.

The median age of the participants was 55 years (80% males). The two groups were well matched in terms of stage, sites of disease and operability status. The patients were followed for a minimum of 24 months from the date of inclusion in the study. Intention to treat analysis was carried out on all the 501 patients who were initially randomized to the 2 arms. The primary end point was overall survival. The secondary end points were progression free survival (PFS), response rates, safety analysis and quality of life analysis. The study was powered to 91% to detect a 15 month increase in median survival in the TPF arm.

The main findings of the study are summarized in table 1.

Median as well as progression free survival was significantly improved in the TPF group. Among those with unresectable tumours, the median survival was 40 months in the TPF group and 21 months in the PF group. The median time to progression of disease was 14 months in the PF group while the same was not reached in the TPF group. Hazard ratio for death was 0.70 (p=0.006). Treatment failures were also more in the PF group vs. the TPF group (45% vs. 35%; p=0.01)- most of these were locoregional failures (38% vs. 30% p=0.04). Regarding toxicities, Neutropenia and infectious complications were more in the TPF arms whereas the PF group had more thrombocytopenia and Stomatitis. Overall, TPF was better tolerated with fewer treatment delays and toxic deaths.

The study authors concluded that TPF was superior to PF as induction chemotherapy in locally advanced SCCHN. This finding was

Table1: Main findings of the TAX 324 study

	PF N=246	TPF N=255	P Value
Overall response After induction chemotherapy	64%	72%	0.07
Complete responses After induction chemotherapy	15%	17%	0.66
Median over all survival (months)	30	71	0.006
% Progression free survival at 3 years	42	53	0.01
% overall survival at 3 years	42	53	0.01
Total deaths (n)	54	41	P = 0.006
Toxicity Data Grade ¾ %			
Anemia	9	12	0.32
Thrombocytopenia	4	11	0.005
Neutropenia	56	83	<0.001
Febrile Neutropenia/neutropenic infection	15	24	0.4
Stomatitis	27	21	0.14
Treatment delay	65	29	<0.001

Table 2: Neoadjuvant chemotherapy trials with triplet regimes in locally advanced HNSCC

Study	Year	Study design	N	Post induction	Results	Comment
Hitt et al[11]	2005	PPF* vs PF	382	RT alone	TPF improved survival (not significant)	Tolerability improved with PPF
GORTEC study[12]	2006	TPF vs PF	220	RT alone	No effect on survival	TPF improved Organ preservation
TAX 323[10]	2007	TPF vs PF	323	RT alone	TPF# had superior PFS and OS	Tolerability improved with TPF
TAX 324[9]	2007	PPF vs PF	501	CRT^	TPF had superior PFS and OS	Used CRT after induction chemo in both arms

*PPF- Paclitaxel +PF,#TPF-Docetaxel+PF,^CRT concurrent CT+RT

consistent across all subgroups of patients regardless of the primary site of disease, reason for therapy, nodal status, primary tumour stage, and surgical curability.

Comments:

This study establishes that a triplet regimen of Docetaxel +PF is superior in terms of survival as well as in having a better toxicity profile as induction chemotherapy in locally advanced SCCHN. Interestingly, similar conclusions were reached in the TAX 323[10] study, a TPF vs PF trial conducted in locally advanced *unresectable SCCHN (table 2).* Though earlier studies with similar trial designs had demonstrated the safety and tolerability of the triplet regimes[11,12], they were not able to demonstrate a survival benefit.

The TAX 324 trial establishes the superiority of TPF chemotherapy as induction therapy *when compared to PF alone*. However, do we need induction chemotherapy at all? With robust data from multiple randomized trials[13]showing survival advantage from concurrent CT +RT as definitive therapy, the role for induction chemotherapy itself is undecided. Given that using a regimen of PF alone is not superior to using CRT, would the use of a triplet regimen prove to be superior? The results of such trials are eagerly awaited. Till then, it would be presumptuous to make policy decisions to change over from a practice of giving concurrent CRT to that of adding induction chemotherapy for the treatment of locally advanced HNSCC. But what this trial does tell us is that, *if* we decide to use induction chemotherapy it would be safer as well as better to use a triplet regime of TPF rather than PF alone.

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