La Terapia di induzione alla Radioterapia nei localmente avanzati: Quale il punto della situazione?

A cura di Elvio Russi ed Anna Merlotti

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Review

Induction chemotherapy for squamous cell head and neck cancer: A neverending story?

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s u m m a r y

Induction chemotherapy prior to planned definitive local therapy for head and neck squamous cell carcinoma has been studied for at least three decades but the debate on its role is still open. Recent landmark studies, including those presented at outstanding meetings and those still ongoing on induction chemotherapy in different clinical situations, are critically reviewed. Data confirm that a docetaxel, cisplatin and 5-fluorouracil (TPF) based induction chemotherapy may be considered in clinical practice as one of the possible options when a larynx preservation strategy is attempted. On the contrary, current data do not support the use of induction chemotherapy before a planned surgical intervention for advanced oral cavity and oropharyngeal tumors. Currently, for patients with locoregionally advanced unresectable disease, concomitant chemo-radiation remains the standard of care in waiting for results of the few ongoing studies that hopefully will clarify the role of induction TPF before either concomitant chemo-radiation or bio-radiation.

Commento

Alla bellissima revisione del dott. Benasso che ripercorre la storia e la logica evolutiva dell'induzione con spunti di riflessione fatti da chi questa storia l'ha vissuta in prima persona, seguono due articoli molto importanti sull'argomento.

Il primo, una metanalisi fatta sui dati dei singoli pazienti dei 5 trial che hanno confrontano l'aggiunta del taxano (prevalentemente Docetaxel) al 5FU e Platino.

Il secondo lavoro è un editoriale della Forastiere che smonta la necessità e l'utilità di questa metanalisi.

Ma non vogliamo anticipare niente e vi abbiamo riportato le affermazioni salienti.

Crediamo che siano lavori che veramente valgano la pena di essere letti.

Abstract

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Taxane-Cisplatin-Fluorouracil As Induction Chemotherapy in Locally Advanced Head and Neck Cancers: An Individual Patient Data Meta-Analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer Group

Pierre Blanchard, Jean Bourhis, Benjamin Lacas, Marshall R. Posner, Jan B. Vermorken, Juan J. Cruz Hernandez, Abderrahmane Bourredjem, Gilles Calais, Adriano Paccagnella, Ricardo Hitt, and Jean-Pierre Pignon on behalf of the Meta-Analysis of Chemotherapy in Head and Neck Cancer, Induction Project, Collaborative Group

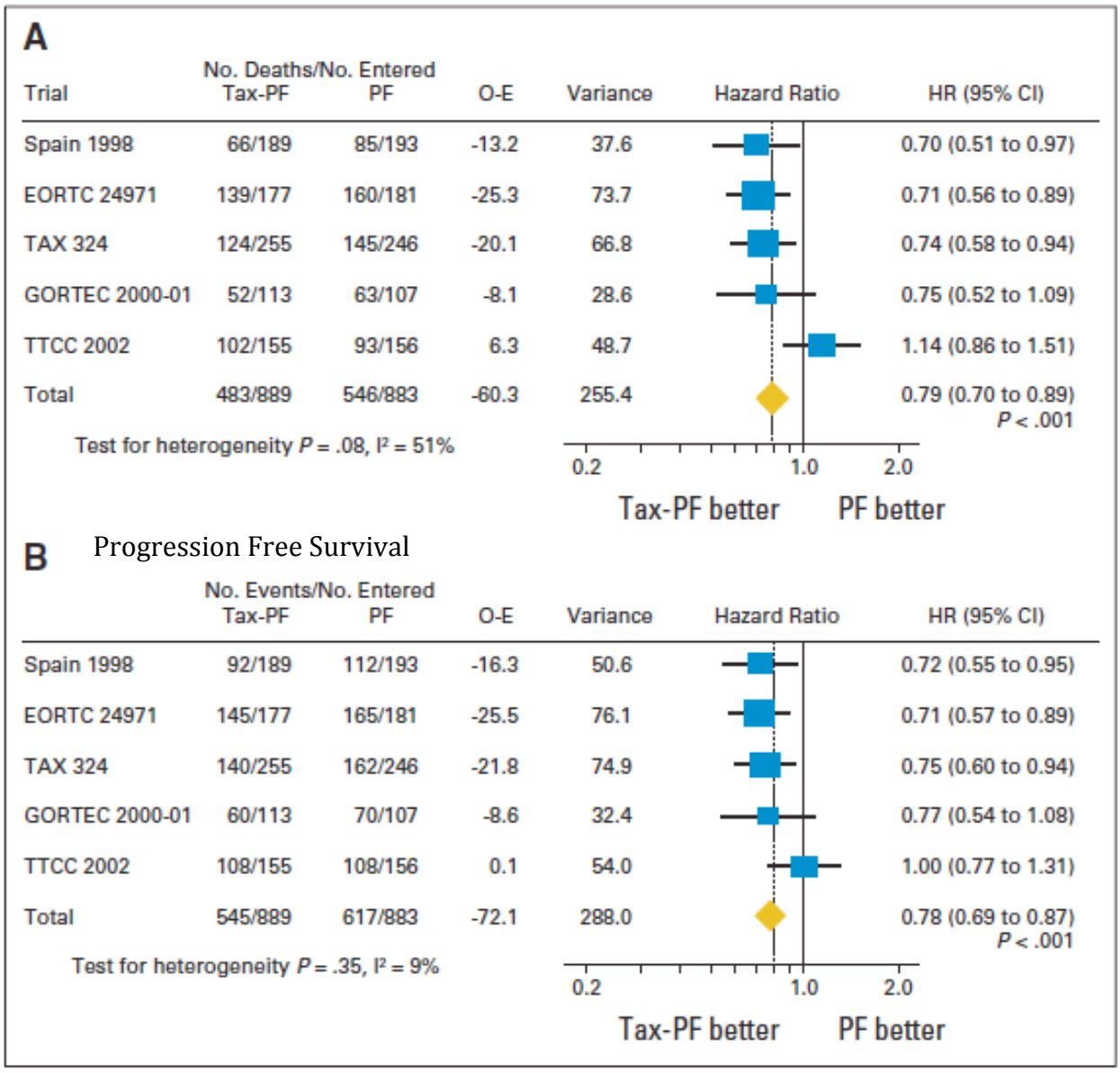
Abstract

Purpose
Cisplatin plus fluorouracil (PF) induction chemotherapy has been compared with taxane (docetaxel or paclitaxel), cisplatin, and fluorouracil (Tax-PF) in randomized trials in locoregionally advanced head and neck cancers (LAHNCs). The aim of this meta-analysis was to study the efficacy and toxicity of Tax-PF and PF and identify differences in outcomes in subsets of patients.

Methods
Five randomized trials representing 1,772 patients were identified. Updated individual patient data (IPD) were retrieved for all trials. The log-rank test, stratified by trial, was used for comparison. Interaction or trend tests were used to study the interaction between covariates and treatment.

Results
Median follow-up was 4.9 years. The hazard ratio (HR) of death was 0.79 (95% CI, 0.70 to 0.89; P _ .001; absolute benefit at 5 years: 7.4%) in favor of Tax-PF. Heterogeneity was significant (P _ .08, I2 _ 51%) and related to one trial. There was no more heterogeneity after exclusion of this trial (P _ .99, I2 _ 0%), and HR of death was 0.72 (95% CI, 0.63 to 0.83) in favor of Tax-PF. There was no interaction between treatment effect and the following patient covariates: age, sex, performance status, tumor stage, or site. Tax-PF was associated with significant reductions of progression, locoregional failure, and distant failure compared with PF, with HRs of 0.78 (95% CI, 0.69 to 0.87; P _ .001), 0.79 (95% CI, 0.66 to 0.94; P _ .007), and 0.63 (95% CI, 0.45 to 0.89; P _ .009) respectively.

Conclusion
This IPD meta-analysis shows the superiority of Tax-PF over PF as induction chemotherapy. Its precise role in the management of LAHNC remains to be determined.



Forest plots for (A) and (B) progression-free survival. Each trial is represented by a square, the center of which denotes the hazard ratio (HR) for that trial, with the horizontal lines showing the 95% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The gold diamonds represent pooled HRs for the overall HRs, with the center denoting the HR and the extremities the 95% CI. The fixed effect model was used. EORTC, European Organisation for Research and Treatment of Cancer; GORTEC, Groupe d'Oncologie Radiotherapie Teˆ te et Cou; O-E, observed minus expected deaths or events; PF, cisplatin, fluorouracil; TAX, Taxotere (docetaxel; sanofi-aventis, Bridgewater, NJ); Tax-PF, taxane, cisplatin, fluorouracil; TTCC, Grupo Espan˜ ol de Tratamiento de Tumores de Cabeza y Cuello.

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JOURNAL OF CLINICAL ONCOLOGY E D I T O R I A L

Induction Chemotherapy Meta-Analysis in Head and Neck Cancer: Right Answer, Wrong Question

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…..This trial was responsible for significant heterogeneity and the follow-up was short. As shown in Table 1, the CI on the hazard ratio for overall survival from the pooled analysis (with and without the TTCC trial) is not much more convincing than the CIs from the TAX3247 and the European Organisation for Research and Treatment of Cancer study 249715 trials. Therefore, this pooled analysis serves to confirm the published results of those two trials that compared two nonstandard induction chemotherapy regimens, but does not provide further insight into the potential benefit of adding induction chemotherapy to definitive standard chemoradiotherapy…..

Table 1. Published Data About Survival in Locoregionally Advanced HNSCC

Study	Primary End Point	Median Follow-Up (months)	OS		Median Survival (months)		2-Year Survival (%)		3-Year Survival (%)		5-Year Survival (%)	
			HR	95% CI	T-PF	PF	T-PF	PF	T-PF	PF	T-PF	PF
TAX324	OS	72	0.74	0.58 to 0.94	70.6	34.8	67	55	62	49	52	42
GORTEC 2000-01	Larynx preservation	36	**0.75**	**0.52 to 1.09**					60	60		
EORTC 24971	PFS	33	0.73	0.56 to 0.94	18.8	14.5	43	32	37	26		
Spain 1998	CR rate	23	**0.70**	**0.51 to 0.97**	42.9	36.8	67	54				
TTCC 2002	PFS, TTF	24	**1.14**	**0.86 to 1.51**	27.0	27.2						
Blanchard et al[11]	**OS**		**0.79**	**0.70 to 0.89**							**42**	**35**
Without TTCC			**0.72**	**0.63 to 0.83**								

NOTE. **Bold type** relates to data from the pooled analysis; otherwise, data are from the original publication.
Abbreviations: CR, complete response; EORTC, European Organisation for Research and Treatment of Cancer; GORTEC, Groupe d'Oncologie Radiothérapie Tête et Cou; HNSCC, head and neck squamous cell cancer; HR, hazard ratio; OS, overall survival; PF, cisplatin, fluorouracil; PFS, progression-free survival; TAX, taxotere; T-PF, taxane-cisplatin, fluorouracil; TTCC, Grupo Español de Tratamiento de Tumores de Cabeza y Cuello; TTF, thyroid transcription factor.

It is also important that the question of conflict of interest be addressed. This meta-analysis was funded by sanofi-aventis, the manufacturer of docetaxel. Four of the five trials included in this metaanalysis tested docetaxel and were also supported by sanofi-aventis. (The fifth, the paclitaxel trial, was supported by Bristol-Myers Squibb.) Although this by itself should in no way impugn the integrity of these investigators or the strength of their science, it is one of many factors that must be considered as we review the data. Perhaps we need to ask whether, in retrospect, this meta-analysis was even necessary.Ameta-analysis of randomized trials is one way to establish Level Ia evidence supporting a clinical observation. But what is the clinical observation? In this case, it is the recognition that taxane, fluorouracil, and cisplatin is a better induction regimen than fluorouracil and cisplatin alone. Given the consistently better response rate for the three-drug regimens seen in the phase III trials, this observation was not in doubt.

What this meta-analysis did not change is the standard of care in HNSCC. Neither the multiple phase III trials nor their meta-analysis are able to establish a new treatment standard from a

comparison of two nonstandard regimens. This point is made by the authors but merits re-emphasis.