Induction chemotherapy with docetaxel and cisplatin versus docetaxel, cisplatin and fluorouracil followed by concomitant chemoradiation in locally advanced squamous cell carcinoma of the head and neck

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Abbreviations

5FU	5-Fluorouracil
ABC	ATP binding cassette
AEs	Adverse events
ATP	Adenosine triphosphate
AUC	Area under the curve
BID	Twice daily
CCDP	Cis-diamminedichloroplatinum (cisplatin)
CCRT	Concomitant chemoradiotherapy
CR	Complete response
CT	Computed tomography
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
ERCC1	Excision repair cross-complementation group 1
GSH	Glutathione
Gy	Gray
HNC	Head and neck cancers
HPV	Human papilloma virus
HR	Hazard ratio
HU	Hydroxyurea
IA	Intra-arterial
ICT	Induction chemotherapy
IPD	Individual patient data
LAHNC	Locally advanced head and neck carcinoma
MACHNC	Meta-analysis of chemotherapy in head and neck cancer
MDR-1	Multidrug resistance gene-1
MECC	Middle-East Cancer Consortium
MRI	Magnetic resonance imaging

MRPs	Multidrug resistance associated proteins
NCRP	National Cancer Registry Program
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PF	Platinum and 5Fluorouracil
PFS	Progression free survival
PR	Partial response
PR	Partial response
QoL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SCC	Squamous cell carcinomas
SCCHN	Squamous cell carcinoma of the head and neck
SEER	Surveillance Epidemiology and End-Results
Tax-PF	Taxane (docetaxel or paclitaxel), cisplatin, and fluorouracil
TLM	Trans-oral laser microsurgery
TPF	Docetaxel/Platinol/5-Fluorouracil
VACSP	Veterans administration cooperative study program

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INTRODUCTION

The administration of chemotherapy in conjunction with radiotherapy in the treatment of patients with locally advanced head and neck carcinoma (LAHNC) has been broadly explored. For many years, chemotherapy has been administered in the adjuvant or neoadjuvant settings and, more recently, concurrently with radiotherapy. The concurrent administration of chemotherapy and radiotherapy has been the most promising approach, given that the dominant pattern of failure with radiotherapy is local and regional relapse. However, the high response rates seen with induction chemotherapy have historically made this approach attractive as well **(Pointreau et al., 2011)**

As many investigators explored altered fractionated radiotherapy, other investigators explored various combinations of chemotherapy and radiotherapy. These chemo-radiotherapy trials included trials of induction chemotherapy followed by radiotherapy (Wirth and Posner, 2007***;*** Brizel and Vokes, 2009) concomitant chemoradiotherapy (CCRT), ***[*(Argiris, 2002)*); (Bourhis et al., 2004) (Bourhis et al., 2007);(Wirth and Posner, 2007)(Wirth and Posner, 2007) (Citrin et al., 2009); (Nuyts et al., 2009)]*** and adjuvant chemotherapy following definitive radiotherapy and/or surgery ***(Munro, 1995).***

In 2000 findings from the Meta-Analysis of Chemotherapy in Head and Neck Cancer study, a meta-analysis of 63 randomized trials on nearly 11,000 patients assessing the impact on survival of adding chemotherapy to loco-regional treatment revealed that adding chemotherapy to loco-regional treatment was associated with an absolute survival benefit of 4% at both 2 years and 5 years, compared with loco-regional treatment alone ***(Pignon et al., 2000).***However, the benefit was statistically significant only with the addition of concomitant chemotherapy to radiotherapy and this approach has emerged as the dominant treatment strategy. Adjuvant and neoadjuvant chemotherapy were not associated with significant benefit. However, all three approaches included trials that did not use optimal chemotherapy regimens. Indeed, 16 of the 31 trials assessed for induction chemotherapy used regimens other than a platinum plus 5-Fluorouracil (PF). When just the 15 trials using PF induction chemotherapy were analyzed, there was a statistically significant overall survival benefit of 5% at 5 years in favor of adding induction chemotherapy to loco-regional treatment ***(Monnerat et al., 2002).*** But again in updates of that analysis, comparisons showed a more pronounced benefit for the concomitant chemotherapy approach than for induction chemotherapy ***(Bourhis et al., 2007), (Pignon et al., 2009).*** Thus,

concomitant chemoradiotherapy has emerged as the most frequently used standard therapy option.

This recent meta-analysis by Pignon and colleagues ***(Pignon et al., 2009)*** of chemoradiotherapy versus radiotherapy alone included an additional 24 trials that were comparisons of induction, concurrent, or adjuvant chemoradiotherapy. The meta-analysis found that there was a benefit of loco-regional control for concurrent chemoradiotherapy compared with induction chemotherapy followed by radiotherapy, but the comparisons should be viewed with caution considering the recent successes with the use of taxane-based induction regimens that were not included in the meta-analysis.

The induction regimen of docetaxel, cisplatin, and 5-fluorouracil has recently shown a survival advantage over cisplatin/5-fluorouracil ***(Posner et al., 2007); (Vermorken et al., 2007)***, in the context of subsequent radiation treatment alone or subsequent radiation treatment and low-dose weekly carboplatin.

The TAX 324 study demonstrated a statistically significant 2-year survival of 68% for the TPF arm vs 55% for the PF arm using the sequential approach but that study employed an unconventional concomitant regimen of carboplatin AUC 1.5

every week. It is possible that the statistically significant difference observed in the TAX 324 study could be due to a suboptimal control arm that is using carboplatin instead of cisplatin for concomitant treatment. This supposition is further supported by the 63% 2-year survival for PF (2 cycles) followed by CCRT (Cisplatin 100 mg/m² at day 1 and day 29) in a retrospective UK study (Bhide et al., 2008) which was superior to the control arm of the TAX 324 study. Currently, there are no data for a head-to-head comparison of carboplatin versus cisplatin in this setting, but the "meta-analysis of chemotherapy in head and neck cancer" most strongly supports the use of cisplatin for concomitant treatment (Blanchard et al., 2011).

A retrospective study by Gupta et al. (2009) retrieved outcome data of 264 patients with Stage III & IV head and neck squamous cell carcinoma, excluding nasopharynx, planned for radical radiotherapy (66–70 Gy) with concurrent weekly cisplatin (30 mg/m²) treated in a single unit between 1996–2004. The efficacy of this regimen was largely comparable to other contemporary series using more intensive CCRT schedules with substantially lower acute toxicity (Gupta et al., 2009).

In another study, thirty-four patients with LAHNC were treated with 3 cycles of induction chemotherapy, consisting of

docetaxel 75 mg/m² and cisplatin 75 mg/m² every 3 weeks, followed 3-4 weeks later by definitive radiotherapy (70 Gy) and concomitant weekly cisplatin 40 mg/m². The protocol was feasible and well-tolerated. The median overall survival (24.4 months) was similar to the matched population in the TPF (Docetaxel/Platinol/5-Fluorouracil) arm of the TAX 324 study (Fountzilas et al., 2009)**.** The role of 5FU in CCRT in the presence of cisplatin has become controversial, and recent guidelines have omitted it in CCRT regimens as it has added toxicity without affecting survival ***(Forastiere et al., 2006).***

Based on the previous studies, the proven advantage of the addition of docetaxel to a platinum based induction chemotherapy, and that cisplatin is the standard drug now for CCRT, the aim of this study is to compare the efficacy and toxicity of induction by 3 cycles by docetaxel/cisplatin followed by CCRT (Conventional EBRT - 66 to 70 Gray (Gy) – and weekly cisplatin 30 mg/m²) with 3 cycles of induction by docetaxel/cisplatin/5FU followed by CCRT (Conventional EBRT - 66 to 70 Gy – and weekly cisplatin 30 mg/m²).

The hypothesis is that in the presence of docetaxel, 5-Fluorouracil (5FU) could be omitted in induction regimens without affecting survival and with a reduction in toxicity.

Aim of the study

The aim of our study is to compare the 1 year progression free survival (PFS), response rate and toxicity of induction by 3 cycles of docetaxel/cisplatin followed by CCRT versus 3 cycles of induction by docetaxel/cisplatin/5FU followed by CCRT in locally advanced head and neck squamous cell carcinoma.

REVIEW OF LITERATURE

Epidemiology

Head and neck cancer comprises a heterogeneous group of cancers at different anatomic locations (Figure 1). These tumors are most commonly found in the oral cavity, the larger pharyngeal area (including the nasopharynx, oropharynx, and hypopharynx), and the larynx. Occasionally, other anatomic sites are involved, such as the paranasal sinuses, lips, salivary glands, and other areas of the head and neck and upper aerodigestive tract. Squamous histology is present in 95% of cases of head and neck cancer ***(Abogunrin et al., 2014).***

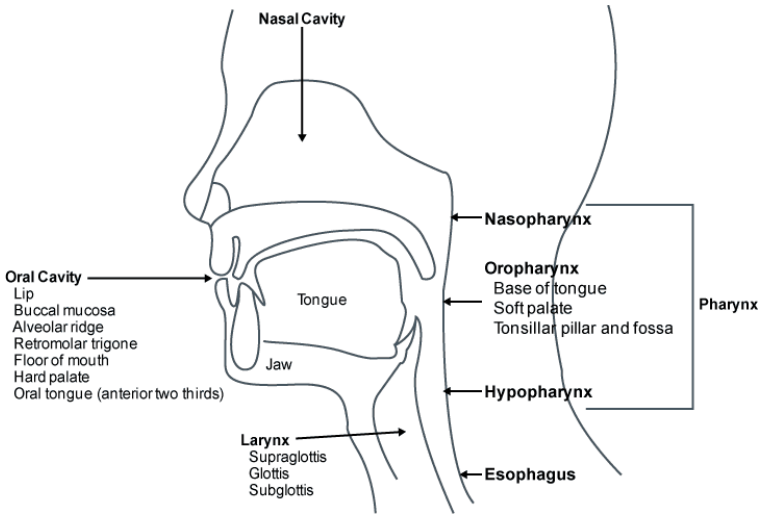

Figure (1). Anatomic site of head and neck cancers. ***(Abogunrin et al., 2014)***

Head and neck cancers (HNC) are a group of malignancies involving oral cavity, pharynx, ear/nose, and larynx. Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer worldwide; approximately 600,000 new cases are diagnosed per year worldwide (International Agency for Research on Cancer. World Health Organisation. Globocan., 2012) and 300,000 deaths are due to HNC (Boyle and Levine, 2008). Ninety percent of HNC is squamous cell carcinomas (SCC) ***(Curado and Hashibe, 2009)*** and generally begins in the mucosal surfaces of the head and neck. in men worldwide. The highest incidences of HNC in the world are found in South Asia, and parts of central and southern Europe ***(Boyle and Levine, 2008)***. By far, the most common risk factors associated with HNC are tobacco and alcohol use with significant interaction observed between the two ***(Blot et al., 1988)***. Other observed risk factors are poor oral hygiene ***(Guha et al., 2007)*** and the human papillomavirus (HPV) 16 in tongue, tonsil and orpharyngeal HNC and, in particular, nonsmoking cases of HNC ***(Kreimer et al., 2005)***.

Within the Middle East, rates of smoking are high ***(El Awa, 2008***) although alcohol consumption is limited. This is especially true for Egypt where smoking rates are increasing for both cigarettes and water-pipe. However, there have been very few studies depicting the magnitude or etiologic factors of HNC in the Middle East and Egypt. Previous hospital-based studies from