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Current attitudes of head and neck oncologists in the United Kingdom to induction chemotherapy for locally advanced head and neck cancer: A survey of centres participating in a national randomised controlled trial

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SUMMARY

Objectives: Induction chemotherapy (IC) followed by chemoradiation (CRT) for locally advanced squamous cell head and neck cancer (SCCHN) remains controversial in the absence of clear evidence to define its role. As part of a prospective, randomised, multicentre study of CRT for stage III/IV laryngeal/hypopharyngeal cancers (ART DECO, CRUK/10/018), we have examined the attitudes of oncologists in the United Kingdom (UK) to IC.

Materials and methods: Head and neck oncologists across the UK who expressed an interest in participating in the ART DECO trial were asked to complete a short written questionnaire designed to identify current UK practice of IC for stage III–IVb SCCHN. Completed questionnaires were returned to the clinical trials office prior to patient recruitment.

Results: Clinicians from twenty-five/48 centres (52.1%) responded. Twenty centres (80%) elected to use IC in the trial. For stage III disease, 80% of centres did not prescribe IC for T1N1 disease and 60% did not offer IC for T3N0 disease. Patients with bulky primary tumours or extensive nodal disease were more likely to receive IC. Thirteen prescribing centres (65%) use 3 drugs (docetaxel, cisplatin, and 5-fluorouracil) compared to 7 (35%) using 2 drugs (cisplatin and 5-fluorouracil). Fifteen centres (75%) prescribed 2 cycles of IC, and 5 (25%) prescribed 3 cycles. There was variation in the dosage for both the 2- and 3-drug regimens.

Conclusion: Results suggest that clinical practice in the UK is currently divided between a 2- versus 3-drug regimen for IC for specific subgroups of patients. A consensus regarding the optimal combinations and dosages is required before further optimization of systemic therapy with other cytotoxics and biological agents is attempted.

Background

The role of induction chemotherapy (IC) prior to definitive loco-regional therapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN) remains controversial [1–3] with no consensus guidelines for its use. A large meta-analysis has shown a modest survival benefit for IC compared to concomitant chemoradiation (CRT) alone, which was not statistically significant (hazard ratio (HR) for death 0.96 (95% confidence interval (CI) 0.9–1.02, $p = 0.18$) [4]. Some authors have proposed the benefit to be related to the reduction in micro-metastatic disease [5–7]. Others have suggested its role should be that of a chemo-selective tool in predicting which patients would benefit from subsequent CRT, rather than surgery, as an organ-preservation strategy [7,8]. Debulking extensive tumour prior to CRT is another potential role. The optimal combination or doses of cytotoxic agents for IC remains unclear. Historically, studies have tested cisplatin and 5-fluorouracil (PF) as induction agents [4], whilst more recent randomised trials have suggested a higher response rate with the addition of docetaxel (T) to PF chemotherapy (TPF) [9–11]. Definitive data from head-to-head comparisons of 2- versus 3-drug IC regimens in the context of gold-standard platinum-based CRT are, as yet, not available in the literature.

The Accelerated Radiotherapy Dose Escalated versus Conventional (ART DECO) (CRUK/10/018) trial is a randomised multicentre study of dose-escalated intensity-modulated radiotherapy (IMRT) versus standard dose IMRT in patients with locally advanced laryngeal and hypopharyngeal squamous cell cancers. The trial opened

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in March 2011 and is currently recruiting patients across the United Kingdom (UK). Investigators entering patients into the study have a choice of using IC prior to CRT according to local practice, with each participating centre stipulating their IC policy in advance. In the trial, randomisation of patients is stratified by treating centre and use of IC to ensure that randomised groups are balanced with respect to use and schedule of IC. Concomitant chemotherapy with cisplatin is mandated unless contraindicated. In this current study, we review the attitudes of head and neck oncologists to the role of IC in the context of the ART DECO trial.

Materials and methods

ART DECO is a phase III randomised controlled trial open in 20 radiotherapy centres in the UK as of 1st March 2013. Patients with locally advanced (stages III–IVb) squamous cell cancers of the larynx or hypopharynx suitable for larynx preservation with CRT or radiotherapy alone are eligible. Patients are randomised in a 1:1 ratio to receive either standard dose intensity-modulated radiotherapy (IMRT) (65 Gray (Gy) in 30 fractions) or dose-escalated IMRT (67.2 Gy in 28 fractions). All suitable patients receive concurrent cisplatin. The primary endpoint is locoregional failure-free rate and secondary endpoints include acute and late toxicity, laryngo-oesophageal dysfunction-free rate, overall survival and quality of life [12]. Many UK centres prescribe IC for patients with locally advanced SCCHN according to local protocols. Clinicians who expressed an interest in the study ($N = 48$) were asked to complete a short questionnaire regarding their intended use of IC. The questionnaire was designed to identify current UK practice of IC for stage III–IVb SCCHN of the larynx and hypopharynx (Fig. 1).

Completed questionnaires were returned to the Cancer Research UK funded Clinical Trials and Statistics Unit at The Institute of Cancer Research prior to the centre being activated as open for recruitment. Staging of laryngeal and hypopharyngeal cancers as per the AJCC Cancer Staging Manual seventh edition (2010) [13].

Statistical analysis

Descriptive statistics were used. Results were collated and presented as percentages to determine prescribing habits and the influence of tumour and nodal stage on the use of IC.

Results

Forty-eight centres expressed an interest in the study. Clinicians from twenty-five centres (52.1%) representing 22 of the 35 UK cancer networks (62.9%) completed the questionnaire. The completion rate of the questionnaires was 100% and all questionnaires were available for analysis.

Overall, 20 centres (80%) stipulated that IC would be used in the context of the trial. For both laryngeal and hypopharyngeal cancers, the intended use of IC varied according to disease stage (Figs. 2 and 3).

Stage III cancers

A large proportion of centres stated that they would not offer IC for stage III larynx (15/25 (56%) for T3N1 and 21/25 (84%) for T1N1 disease) or hypopharynx cancer (13/25 (52%) for T3N1 and 20/25 (80%) for T1N1 disease). Patients with T3 disease were more likely to be prescribed IC (11/25 centres (44%) for larynx and 10/25 (40%) for hypopharynx cancer) than those with T1N1 disease (4/25 (16%) for larynx and 5/25 (20%) for hypopharynx) or T2N1 disease (5/25 (20%) for larynx and 6/25 (24%) for hypopharynx cancer), suggesting that, for stage III disease, a bulky primary tumour is considered higher risk than N1 positive disease.

Stage IVa

Prescribing patterns for stage IVa laryngeal cancer were as follows: 13/25 (52%) centres offered IC for T1N2 disease compared to 18/25 (72%) for T4aN2 disease. For hypopharynx cancer, IC was offered by 14/25 (56%) centres for T1N2 disease and 18/25 (72%) for T4aN2 disease.

Stage IVb

For laryngeal cancer, 16/25 centres (64%) offered IC for T4bN0/N1 compared to 20/25 (80%) for T1–3N3 disease. For hypopharynx, 17/25 (68%) centres prescribed IC for T4bN0 disease and 20/25 (80%) for T1–3N3 disease, suggesting a similar attitude to prescribing IC for larynx and hypopharynx cancers.

All centres prescribing IC stated that they would use IC for N3 disease (except one centre, which would not prescribe IC for T4aN3 and T4bN3 cancer). The use of IC for T4b disease was similar across all nodal stages (17/25 (68%) centres for N0/N1 disease to 19/25 (76%) for N2/N3 disease.

PF vs TPF

The majority of centres (13/20 (65%)) said that they would use a 3-drug regimen with TPF, with 7/20 (35%) using PF (Table 1). Fifteen of the 20 centres (75%) prescribed 2 cycles of IC, and the remaining 5 (25%) centres prescribed 3 cycles. The intended chemotherapy combinations and doses are summarized in Table 1. For centres prescribing TPF chemotherapy, the dose of T was constant at 75 mg/m^2 on day 1 (D1). The dose of P varied from 75 to 100 mg/m^2 on D1 and the dose of F varied from 3000 to 5000 mg/m^2 per cycle.

Discussion

This survey demonstrates the substantial use of IC in UK cancer networks. The rationale for the use of IC is based mainly on the premise that the efficacy is improved in well vascularized, untreated tumours (due to better drug delivery), micrometastatic disease can be treated upfront, and tumour response and shrinkage can occur prior to radiotherapy or surgery [14]. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) study demonstrated a non-statistically significant 2% survival benefit at 5 years with IC [15]. This may explain the lack of enthusiasm for IC amongst some clinicians. It is important to note, however, that 16 of the 31 trials included in the meta-analysis assessing IC utilized suboptimal chemotherapy regimens without PF. When analyzing the 15 trials that did use induction PF, a statistically significant overall survival benefit at 5 years in favour of IC was demonstrated (HR 0.88 (95% CI 0.79–0.97) [15,16]. As a result, proponents of IC have been comfortable with the use of this combination in the pre-taxane era.

One fifth of UK centres completing the survey do not subscribe to the use of IC. Long-term follow-up results from the RTOG 91–11 trial showed improved larynx preservation with a concomitant strategy over PF followed by RT (HR 0.58, $p = 0.005$) [17]. Therefore, CRT remains a standard therapy approach for larynx preservation with no clear guidance on the strategy following IC. It is important to note, however, an increase in non-cancer related deaths in the CRT arm after 4.5 years despite no increase in late toxicity. The trial was conducted almost 2 decades ago using conventional RT techniques which may have contributed to complications such as