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From chemoprevention and organ preservation programmes to postoperative management: major achievements and strategies of the EORTC Head and Neck Cancer Group

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Abstract

The purpose of this article is to review the most significant results of the clinical studies conducted in the past two decades by the EORTC Head and Neck Cancer Group (HNCG). As for phase III trials, the HNCG investigated, besides the efficacy of chemopreventive drugs, the impact of cytostatic agents on various therapeutic targets, in combination or not with surgery and chemotherapy. These targets were: (a) chemo-prevention in curatively treated early stage disease; (b) organ preservation programmes in patients with operable tumour, comparing immediate surgery versus first-line chemotherapy; (c) postoperative management of locally advanced tumours, comparing radio-chemotherapy versus radiotherapy alone. Other phase II and phase III studies were also completed to investigate drug activity in advanced and/or recurrent head and neck squamous cell and adenoid cystic carcinomas. The present article will also analyse the strategies developed within the Group in the field of translational research.

Keywords: Head and neck cancer; Radiotherapy; Surgery; Chemotherapy; Phase II study; Phase III study; Randomised study; Molecular biology

1. Introduction

Over the last three decades, it has been repeatedly substantiated that the good results yielded by single modality surgical and radiotherapeutic treatment for early stage head and neck cancer are by far less satisfactory when applied to advanced disease. As regards radiotherapy, for instance, one approach is to use biologically-based altered radiation fractionation schedules, which range from hyperfractionation (HF) to accelerated fractionation (AF) [1,2]: compared with conventional fractionation, both of them increase indeed loco-regional control rates by about 15%, with a better therapeutic index for HF.

Beyond these radiotherapy schedules, the other major experimental approach to the treatment of advanced head and neck cancer is to combine chemotherapy and radiotherapy. Various chemotherapy settings, ranging from neo-adjuvant delivery prior to surgery or radiotherapy, to concurrent radio-chemotherapy have been investigated in the last 15 years, with a large burden of data now available for the late results of these multidisciplinary approaches.

In the last two decades, special attention has been paid to patients whose disease can be surgically removed: whilst surgery followed by adjuvant radiotherapy remains the management favoured in most institutions, much clinical research has nevertheless

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been focused on improving non-surgical treatment with the objective of preservation of form and function.

The purpose of this article is to review the most significant results of the clinical studies conducted in the past two decades by the EORTC HNCG in head and neck oncology, including chemoprevention, organ preservation programmes, drug efficacy clinical testing and quality assurance. It will also analyse the strategies developed within the Group in the field of translational research.

2. Clinical studies: materials and methods

The trials issued, over the last two decades, by the HNCG are classified and illustrated in Table 1. As regards the therapeutic targets, the HNCG pursued three distinct avenues of research: (a) clinical evaluation of new treatments in head and neck cancer patients, particularly cytostatic drugs; (b) research on chemoprevention of second primaries; (c) research on organ preservation, particularly for pharyngeal and laryngeal cancers, as a result of neo-adjuvant chemotherapy.

Clinical investigations included both phase II and phase III studies (Tables 2–5). The major phase III trials conducted by HNCG were EUROSCAN, EORTC Trial 24891 and EORTC Trial 22931.

EUROSCAN was a phase III European *chemoprevention* study in curatively treated early stage head and neck (oral, larynx) and lung cancer patients which was initiated in 1988. The study design included two approaches to combat the problem of secondary tumours: early detection and (chemo)-prevention. From the second year following curative treatment, patients were randomised in a 2×2 factorial design to receive the following chemopreventive treatment: (a) retinyl palmitate 300,000 IU daily during 1 year and half this dose during the second year, (b) N-acetylcysteine 600 mg during 2 years, (c) treatments (a) and (b) simultaneously, or (d) no chemopreventive treatment. Between 1988 and 1994, 2592 patients were randomised, of which 2446 were eligible (1076 larynx, 490 oral and 1026 lung cancer patients). The primary study endpoints were second primary tumours, local and regional recurrence, and survival. The main objective of the trial was to test the benefit of chemoprevention in preventing secondary tumours in patients curatively treated for head and neck and lung cancer.

More recently, the HNCG closed two phase III trials, both in an neo-adjuvant chemotherapy (NACT) and in

Table 1
Main targets of the HNCG clinical research

Type of study	Modality investigated	Example of therapeutic targets
Phase II	Cytostatic drugs	*Drug activity*: advanced and/or recurrent H&N squamous cell and adenoid cystic carcinomas
Phase III	Cytostatic drugs	*Organ preservation programme*: immediate surgery versus first-line chemotherapy
Phase III	Multimodal management	*Postoperative management:* radio-chemotherapy versus radiotherapy alone
Phase III	Chemo-preventive drugs	*Chemo-prevention:* curatively treated early stage diseases

H&N, head and neck; HNCG, Head and Neck Cancer Group.

Table 2
Phase II studies in advanced or recurrent head and neck squamous cell carcinomas

	Compound	
	10-EdAM	Piramycin
Year/pts	1992/44 pts	1994/26 pts
Schedules	80 mg/m^2/week 10% increments	70 mg/m^2/every 3 weeks
Outcome	CR + PR: 24%	PR: 1/26
Toxicity	Stomatitis: 73% Dermatitis: 25% Gr IV granulocytopenia: 9%	Gr IV leucopenia: 62% Gr IV thrombocytopenia: 8% Gr IV anaemia: 15% Severe infection: 8%
Conclusions	Same antitumour activity as MTX Higher toxicity than MTX Safe dose: 70 mg/m^2/week	Not recommended as second-line treatment
Authors	Schornagel and colleagues [6]	De Mulder and colleagues [7]

pts, patients; CR, complete response; PR, partial response; Gr IV, grade IV; MTX, methotrexate.

a concomitant chemo-radiotherapy setting, the results of which are considered as major breakthroughs by the head and neck oncology community.

As for the NACT trial (EORTC 24891), 202 patients with T2–4 N0–3 pyriform sinus squamous cell carcinoma, amenable to surgery, were randomly assigned, from 1990 until 1995, to receive either immediate surgery with postoperative radiotherapy (50 or 70 Gy) or induction chemotherapy (cisplatin, 100 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2/days 1–5). In this latter arm, after the second course of chemotherapy (a) complete responders were eligible for an immediate radiotherapy treatment, (b) partial responders received a third course followed by radiotherapy and (c) non-responders underwent surgery and postoperative radiotherapy.

As for the concurrent radio-chemotherapy trial (EORTC 22931), the HNCG investigated its efficacy in a postoperative setting model, for patients presenting with either oral cavity, oropharyngeal, hypopharyngeal or laryngeal carcinoma, T3-4, any N, M0 *or* T1-2, N2-3, M0 *or* T1-2, N$<$2 and high risk factors (insufficient resection margin, perineural involvement, vascular embolisms, extracapsular spread). This study was conducted by the HNCG and the Radiotherapy Group. From 1994 until October 2000, 334 patients were randomly assigned to either radiotherapy alone (RT), up to 66 Gy in 33 fractions, or radio-chemotherapy, using the same RT schedule combined with three courses of cisplatin, 100 mg/m^2, on D1, D22 and D43.

The development of this clinical research within the HNCG also implied the set-up of a long-term Quality

Table 3
Phase II studies in advanced/recurrent adenoid cystic carcinomas

	Compound	
	Epirubicin	Mitoxantrone
Year/pts	1993/20 pts	1996/36 pts
Schedules	(a) 30 mg/m^2/week (b) 90 mg/m^2/3 weeks	30 mg/m^2/every 3 weeks
Outcome	CR + PR: 10% Obj. improv.: 30%	PR: 12% Obj. improv.: 30%
Toxicity	Alopecia: (a) 84%, (b) 93% Emesis: (a) 63%, (b) 85% Stomatitis: (a) 21%, (b) 14%	Nausea: 62% Vomiting: 29% Hair loss: 53% Mucositis: 40%
Conclusions • symptomatic pts • rapidly growing disease	Reversed to:	Modest antitumour activity
Authors	Vermorken and Colleagues [8]	Verweij and colleagues [9]

pts, patients; CR, complete response; PR, partial response; Obj. improv., objective improvement.

Table 4
Chemotherapy phase III studies in H&N SCC (I)

	Tumour site	
	Oral cavity/oropharynx	H&N all sites
Year/pts	1991/222 pts	1994/382 pts
Study design	Immediate surgery (A) versus intra-arterial pre-op CR (B)	CDDP-MTX-BLEO-VINC(CABO) versus CDDP-5-FU (CF) versus CDDP (C)
Outcome	• Median survival: 3 (A) versus 7 (B) years in floor of mouth ca pts • No significant difference in other sites	• Overall RR: CABO: 34%; CF: 31%; C: 15% • No difference in PFS, OS
Quality of life	Overall CT toxicity: 12% 1 treatment-related death	Haematological and non: worse in multidrug regimes
Conclusions	Intra-arterial CT increase local control and survival in pts with floor of mouth SCC, not in other sites	CABO: higher RR, not OS Higher toxicity of multidrug regimes
Authors	Richard and colleagues [10]	Clavel and colleagues [11]

pts, patients; CT, chemotherapy; H&N SCC, head and neck squamous cell carcinoma; RR, response rate; 5-FU, 5-fluorouracil; CDDP, cisplatin; MTX, methotrexate; PFS, progression-free survival; OS, overall survival.

Assurance Programme which not only encompasses the various trial- and patient-orientated control procedures, but also monitors the evolution of department infrastructure and environment, in more than 40 centres actively participating to the HNCG studies. Comprehensive Quality Assurance Programmes are of critical importance for a successful development of these new strategies. Beyond the trial- and patient-orientated issues, such as individual case reviews and, for radiotherapy-based protocols, dummy runs, various electronic surveys will be conducted among the HNCG institutes, with particular attention to department infrastructure and human resources. On-site visits are also foreseen in the framework of the future trials, especially for organ preservation studies.

3. Results

Various important messages emerged from the various studies conducted, by the HNCG, in the 1980s and early 1990s. Listed below are some of the most significant contributions.

3.1. Major phase III trials

3.1.1. EUROSCAN

At a median follow-up of 49 months, it was found that neither retinyl palmitate nor N-acetylcysteine were able to reduce significantly the incidence of second primary cancers or loco-regional recurrence in patients with early stage disease, treated with curative intent [3]. Indeed, no significant difference was observed between the event-free survival in the 1290 patients randomly assigned to receive retinyl palmitate (465 events) compared with the 1283 assigned to receive no retinyl palmitate (451 events), with a relative risk of 1.03 (95% Confidence Interval (CI): 0.90–1.17). Similarly, no difference (relative risk of 1.03 and 95% CI: 0.91–1.18) was seen when comparing patients randomised to N-acetylcysteine (468 events in 1285 patients) to those assigned to no N-acetylcysteine (448 events in 1288 patients).

3.1.2. Trial 24891

In the induction-chemotherapy arm, complete response was seen in 52 (54%) of 97 patients with local disease only and in 31 (51%) of 61 cases with regional disease. Treatment failures at local, regional and second primary sites occurred at approximately the same frequencies in the immediate surgery arm (12, 19 and 16%, respectively) and the induction-chemotherapy arm (17, 23 and 13%). There were fewer failures at distant sites in the induction-chemotherapy arm than in the surgical arm (25 versus 36%; $P = 0.041$). The median survival was 25 months in the immediate-surgery arm and 44 months in the induction-chemotherapy arm and since the observed hazard ratio was 0.86 (logrank test, $P = 0.006$), which was less than 1.43, the two treatments were judged to be equivalent. The 3- and 5-year estimates of retaining a functional larynx in patients treated in the induction arm were 42 and 35%, respectively. These results led the HNCG to activate an ongoing phase III study comparing NACT with a regime alternating radio- and chemotherapy (Trial 24954).

3.1.3. Trial 22931

In terms of efficacy results, disease-free was the primary endpoint and the four secondary endpoints were

Table 5
Chemotherapy phase III studies in H&N SCC (II)

	Tumour site	
	H&N all sites	H&N all sites
Year/pts	1998/124 pts	1987/185 pts
Study design	MTX (*n*: 28): 40 mg/m^2 (A) Paclitaxel (*n*: 27): 3-h 175 mg/m^2 (B) Paclitaxel (*n*: 27): 24-h 175 mg/m^2 (C)	CDDP-MTX-BLEO-VINC (CABO) versus ABO
Outcome	• 13 responses observed in 76 assessable patients • Dose reduction, Gr IV neutropenia and febrile neutropenia significantly more frequent in (C);	• Overall RR: CABO: 16%; ABO: 5% • No difference in PFS, OS
Quality of life	Gr III-IV mucositis significantly more frequent in (A)	Haematological toxicity: not worse in CABO; GI toxicity significantly higher in CABO
Conclusions	All three arms show antitumour activity; the 24-h paclitaxel schedule induces more frequently serious adverse events	Role of cisplatin confirmed in H&N ca management
Authors	Vermorken and colleagues [13]	Clavel and colleagues [14]

H&N SCC, head and neck squamous cell carcinoma; pts, patients; Gr IV, grade IV; RR, response rate; PFS, progression-free survival; OS, overall survival; GI, gastrointestinal.

overall survival, time to progression, loco-regional control and late effects in normal tissues. The final analysis of this study will be done during the first semester of 2002. Interim analysis showed that, in the experimental arm, grade 3-4 functional mucosal reactions were significantly more frequent than during RT (42 versus 21%; $P=0.0004$). However, there was no significant difference in terms of objective mucosal reactions ($P=0.21$) [5]. As regards the compliance to the radiotherapy schedule, no imbalance was seen between the two arms in patients for whom the dose had to be reduced by more than 10%. Likewise, taking the same cut-off of 10% for the overall treatment time, there were only marginal differences between the experimental and control arms, but it was worth noting that around 10% of the patients experienced a significant prolongation of their treatment: their overall treatment time was indeed increased by more than 20% compared with that prescribed by the protocol. The postoperative setting was also shown to reduce the compliance to the chemotherapy protocol: while approximately 65% successfully completed two courses of chemotherapy, the full compliance rate dropped to 50% after the third and final course. As regards haematological toxicity, grade 3-4 leucopenia and granulocytopenia was observed in 14 and 11% of the cases, respectively. As for the non-haematological toxicity, while around 10% experienced severe emesis, grade 3 infection was observed in 5% of the cases receiving chemotherapy.

3.2. Phase II studies

The results of these phase II studies, as well as those of other chemotherapy phase III trials are illustrated in Tables 2–4, and can be summarised as follows:

- Phase II studies in advanced/metastatic Head and Neck squamous cell carcinomas:
  - 10-EdAM shows the same activity as methotrexate, at a safe dose of 70 mg/m^2/week [6].
  - Piramycin is not recommended as second-line treatment because of high toxicity [7].

- Phase II studies in adenoid cystic carcinomas:
  - Epirubicin has to be reserved to rapidly growing tumours and/or symptomatic patients [8].
  - Mitoxantrone shows only modest anti-tumour activity [9].

3.3. Drug efficacy: other phase III trials

The results of these phase III studies, as well as those of other chemotherapy phase III trials are illustrated at Tables 4–6, and can be summarised as follows:

- Compared with immediate surgery, intra-arterial chemotherapy increases local control and survival in patients with carcinoma of the floor of mouth [10].
- Compared with CDDP alone, multidrug regimes (CDDP-MTX-BLEO-VINC (CABO) versus CDDP-5FU (CF) versus CDDP (C)) increase response rates but not survival in patients with advanced head and neck squamous cell carcinomas [11], indicating that, outside the framework of prospective clinical studies, the HNCG promotes single agent methotrexate as standard therapy.

Table 6
HNCG phase III trials: published efficacy results

	Tumour site	
	H&N all sites	Hypopharynx T2-4 N0-3
Year/pts	1995/264 pts	1996/202 pts
Study design	Edatrexate (EDX) versus methotrexate (MTX)	Immediate surgery versus induction CT
Outcome	Overall response rate: • EDX: 21% • MTX: 10%	3-year DSF: 25 versus 27% D.M.: 26 versus 25% ($P<0.04$)
Quality of life	Five treatment-related deaths (4 EDX, 1 MTXD)	Larynx preserved in 50% of pts alive at 3 years in the induction of CT arm
Conclusion	Similar activity for both antifolates EDX more toxic than MTX No recommended for palliation	Larynx preservation: safe Reduction in DM rate after induction CT
Authors	Schornagel and colleagues [12]	Lefèbvre and colleagues [4]

pts, patients; H&N, head and neck; CT, chemotherapy.

- Edatrexate is not recommended for palliative treatment of head and neck carcinomas because of a higher toxicity than methotrexate [12].
- In the study comparing methotrexate to two schedules of paclitaxel (3-h versus 24-h, all three arms showed antitumour activity whilst the 24-h paclitaxel schedule induced more frequent serious adverse events [13].
- The study comparing CDDP-MTX-BLEO-VINC (CABO) versus MTX-BLEO-VINC (ABO) showed the important role of cisplatin in the therapeutic management of head and neck cancers [14].

3.4. Quality Assurance (QA) Programme

Besides the individual case review performed, in the framework of the QA Programme for trial 22931, the HNCG also carried out a clinical and radiotherapy chart review for patients registered in an organ preservation study (Trial 24954). In this trial, a sequential chemo-radiotherapy regime with 2–4 courses of cisplatin and 5-fluorouracil was compared with an alternating chemoradiotherapy schedule in patients with operable, locally advanced carcinomas of the hypopharynx or larynx. Methodological difficulties in clinical research were actually well demonstrated by the results of this individual case review performed at the Institut Gustave Roussy at Villejuif. It results indeed that: (a) time and dose factors applied by the investigators are in good compliance with protocol guidelines; (b) dose homogeneities within the target volume are shown to be affected by major deviations in more than 25% of the reviewed cases; (c) the quality of the documentation sent to the QA reference centre is poor and/or complete for disease- and treatment-related parameters. Since this individual case reviews indicated that, among participating centres, there exist large variations in compliance to the protocol guidelines clear recommendations were developed.

4. Translational research: genetic alterations and response to treatment

Among all induction therapy regimes, neoadjuvant cisplatin-based chemotherapy has been the most widely used in the last decade for organ preservation or unresectable disease, in advanced stage head and neck cancer. The fact that responders to neo-adjuvant chemotherapy do significantly better then non-responders has triggered the interest for the use of predictive tests, especially as regards the chemosensitivity variations in individuals, that may be related to differences in the molecular pattern of these tumours.

Tumour cell death is largely by apoptosis and the *TP53* gene has a major influence on this. Alterations of the *TP53* gene have been shown to contribute to carcinogenesis and drug resistance. In *in vitro* studies loss of wild-type *TP53* function is well known to inhibit the apoptotic pathway. In head and neck cancer patients, *TP53* gene mutations and allelic losses at 17p are actually one of the most common genetic alterations and since this tumour suppressor gene plays a crucial role in cell cycle control and apoptosis in response to DNA, its mutations could be associated with a poor response to chemotherapy and/or radiotherapy in a significant number of patients [15].

As a matter of fact, the role of apoptosis-regulating oncoproteins in defining the response to cytotoxic therapy still remains poorly understood and the role of p53 protein overexpression (which is associated with *TP53* gene mutations) in predicting the response to chemotherapeutic agents and survival rates is not clear at all.

These uncertainties reported in detail for p53 are actually typical of many other controversies regarding the significance of various modifications of gene expression in head and neck carcinomas. Some of these genes nevertheless have been shown to be worth investigating in uniform clinical models such a *MIB1* and *PCNA* for cell cycle and proliferation, *p16* [16] for the inactivation of the Rb pathway and the control of the G1 checkpoint and *GLUT1* [17] with respect to glucose transport, oxygenation conditions and growth maintenance.

The predictive value of biological markers can be tested when at least three conditions are met: the clinical model must be homogeneous, the treatment must be uniform, and clinical data must be prospectively collected according to standardised methodologies. Actually these requirements are met by the EORTC trial 24981. As mentioned above, in this study, patients amenable to surgery were randomly assigned to receive either immediate surgery with postoperative radiotherapy (50 or 70 Gy) or induction chemotherapy (cisplatin, 100 mg/m^2 on day 1 and 5-fluorouracil (1000 mg/m^2/days 1–5). In the induction chemotherapy arm, tumour samples were collected in more than 80 patients prior to the chemotherapy treatment. Samples were stored in three institutions (Lille CHU, Lille O. Lambret, and Villejuif IGR). Both the tumour chemoresponsiveness in first-line treatment and disease outcome were documented prospectively and possible correlations with laboratory data will be investigated in the current project, where we will investigate if biological markers can be used to select patient subgroups likely to respond to intensive chemo-radiation programmes.

5. Conclusions

In the light of the results generated throughout the last two decades, the HNCG will favour various

strategies aimed at increasing the standards of care in head and neck oncology. It will promote translational research, analyse the role of novel organ preservation programmes. The HNCG will also continue to test the antitumour activity of new drugs (cytotoxic and non-cytotoxic) and to investigate the impact of dose intensity modulation in radiotherapy and chemotherapy, both as single modalities or in combination.

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