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Head and Neck Cancer: Prognostic Factors for Response to Chemotherapy

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INTRODUCTION

CHEMOTHERAPY FOR cancer of the head and neck is now a major therapy alongside surgery and radiotherapy. Chemotherapy is important in all head and neck tumours whatever the histological type: squamous cell carcinoma, undifferentiated carcinoma of nasopharynx, or lymphoma. Tumours of the salivary gland and adenoid cystic carcinomas are uncommon diseases, but may eventually be treated by chemotherapy as well.

SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

Patients with advanced head and neck squamous cell carcinoma have a very poor prognosis with a five-year survival of less than 30%. Most of the patients die from local disease due to recurrence, while some 6–7% develop metastases [1]. More than 20% of the patients develop a second primary, usually in the pharynx, larynx, bronchus or oesophagus. The rate of second malignancy is clearly related to the behaviour of the patients. With reductions in the intake of tobacco and alcohol, the rate declines.

In this review, we will consider chemotherapy for recurrent and metastatic disease, chemotherapy as part of a combined strategy for previously untreated advanced disease and second malignancy chemoprevention. Because the response to up-front chemotherapy is of major importance, the prognostic factors for response are crucial.

CHEMOTHERAPY FOR RECURRENT AND METASTATIC SQUAMOUS CARCINOMA

Monochemotherapy. Methotrexate (MTX), cisplatin (C), bleomycin (BLM) 5-fluorouracil (5-FU) and vincristine (VCR) are the most active drugs [2]. New drugs have some activity and include vindesine (VDS) and hydroxyurea (HU). Comparative studies have examined a potential dose-response effect for methotrexate, but so far methotrexate in the form of 40 mg/m^2 weekly is the well accepted standard monochemotherapy. New analogues such as 10-edam have similar activity.

Polychemotherapy. Many combinations have been evaluated in this subset of patients. Response rate with polychemotherapy is about 50% including a clinical complete response of about 10% [3]. Several authors reported a response rate higher with polychemotherapy than with monochemotherapy. Cisplatin-containing polychemotherapy is more active than non-cisplatin-containing regimens [4]. 5-FU was found to potentiate the activity of cisplatin *in vitro* and cisplatin/5-FU was demonstrated to be a safe and active manageable combination [5]. The EORTC have conducted a three arms randomised study comparing CABO (cisplatin, methotrexate, bleomycin, vincristine), CF and cisplatin alone. Both combinations were more active than cisplatin alone whilst no difference was found between CABO and CF.

The duration of response is still disappointing with a median of 4–6 months, whichever chemotherapy combination is used. Among many prognostic parameters, only performance status is associated with a high response rate to chemotherapy. Previously untreated patients fare significantly better than previously treated patients (surgery with or without radiotherapy). A high response rate, a short duration of response and a better activity in previously untreated patients are the rationale for a combined strategy including CT at an earlier stage.

COMBINED TREATMENT—CHEMOTHERAPY AND LOCOREGIONAL TREATMENT

Chemotherapy is now included in most of the therapeutic strategies for locally advanced squamous cell carcinoma, T3 and T4.

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Neoadjuvant chemotherapy as upfront treatment

The benefit of neoadjuvant chemotherapy is still controversial. It gives a high response rate, but so far, the impact on overall survival is very disappointing.

Chemotherapy may produce a very high response rate as high as 93% including a 54% clinical complete response rate [6].

The long term survival is closely related to the response and to the quality of response (CR > PR > stable and no response). Unfortunately, so far very high activity does not translate into longer survival as long as analysis includes all patients treated.

On the other hand, whether or not complete responders might be locally treated by radiotherapy alone is still under investigation. It is a major issue for laryngeal tumours where no laryngectomy is performed in about 30% of these responding patients [7], and the impact on quality of life is obvious.

Adjuvant chemotherapy

Several randomised trials failed to demonstrate any advantage of adjuvant chemotherapy in term of survival. The Head and Neck Contract Program compared induction chemotherapy plus standard therapy to induction chemotherapy plus standard therapy plus adjuvant therapy for 6 months. No difference in disease-free survival or survival, but a lower metastatic rate in the adjuvant arm was found [8, 9].

Chemotherapy plus radiotherapy

Many chemotherapy agents have been shown to enhance the radiotherapy therapeutic index: bleomycin, hydroxyurea, 5-FU, mitomycin have been extensively tested. To summarise, bleomycin, 5-FU and mitomycin have been demonstrated to improve outcome compared with radiation therapy alone. New studies showed that cisplatin is a very good candidate as radiosensitiser. Many trials showed an improved local control with a high rate of toxicity but failed to demonstrate any benefit in survival [10–13].

Only limited subsets such as non-keratinising squamous cell carcinomas have longer survival in the concomitant chemotherapy plus radiotherapy combination [20].

On the other hand new approaches using different fractionations and alternating chemotherapy and radiotherapy have found a significant advantage for progression free survival and survival [21].

RESPONSE TO CHEMOTHERAPY—PROGNOSTIC FACTORS

From this short overview of the activity of chemotherapy in head and neck squamous cell carcinoma, it is clear that it is a very efficient treatment resulting in complete including pathological, responses. Nevertheless the overall survival is not significantly improved by chemotherapy. Thus it is very important to define which patients are going to respond to chemotherapy, since we know that only this subgroup of patients might be improved by the treatment. We also know that a high response rate and complete response are associated with improved local control at the end of the combined therapy and also with longer survival. Therefore, we have to know what are the prognostic factors in term of response to chemotherapy. The second question is: if response to chemotherapy is a major indicator for long term outcome, how can we increase the response rate—especially the complete response rate—induced by neoadjuvant chemotherapy?

Table 1. T3 versus T4 in relation to response to treatment after neoadjuvant chemotherapy

Ref.	Author	Year	T3 versus T4
13	Wolf *et al.*	1984	T3 > T4
18	NCI Contract Program	1987	T3 > T4
14	Jacobs *et al.*	1987	T3 > T4
15	Pinnaro *et al.*	1988	T3 > T4
16	Ildstad *et al.*	1989	T3 > T4
17	Hong *et al.*	1981	T3 > T4, $P = 0.03$
18	Perry *et al.*	1981	T3 > T4, $P = 0.05$
19	Price and Hill	1986	T3 > T4, $P = 0.008$

Prognostic factors

(a) *The size of tumour.* Many authors compared T3 and T4 lesions in regard to response to chemotherapy. Despite the fact that TNM classification might not be accurate for some specific sites, it is clear that in most reports, patients with T3 lesions fare better than those with T4 lesions (Table 1).

(b) *The nodal status* is also important for predicting the response to chemotherapy (Table 2). If we consider the local control and survival after induction chemotherapy in relation to initial nodal status at the presentation, we find the same significant trend in favour of patients with N0/N1 disease (Table 3).

(c) *The site of primary* has been extensively reported as a potentially significant prognostic factor. Some reports are summarised in Table 4, but the results are still controversial. In contrast, there is a clinical consensus that a higher response rate is seen in rapidly growing "cauliflower-like" tumours than in flat, infiltrating, ulcerated tumours.

(d) *The performance status* is a major prognostic factor (table 5). These analyses, however, may be hampered by small numbers, since in many combined treatment protocols only patients with good perform status are eligible for entry.

(e) *The quality of response to chemotherapy.* Although CR patients have a better outcome than PR patients in term of survival (Table 6), we know that clinical assessment is not a good tool for evaluation of CR The best assessment is pathological response, which means that a surgical procedure has to be done for evaluation of response. For many investigators, cytological aspiration is insufficient and sometimes misleading. Thus pathological complete response is clearly the ultimate goal for neoadjuvant chemotherapy.

Table 2. Local control and survival in relation to initial nodal status (at the presentation) after induction chemotherapy

Ref.	Author	Year	No. of patients	Remarks
18	Hong *et al.*	1981	55	N0–1 > N2–3 (NS)
22	Schwert *et al.*	1983		
23	Weaver *et al.*	1984	N.A.	Initial nodal status: best predictor of CR
24	Al-Sarraf	1988		
6	Al-Sarraf	1984	159	CR: T4-NO-MO 89% vs. T4-N3-Mo 25%

NA = not applicable, NS = not significant, CR = complete response.

Table 3. Local control and survival in relation to initial nodal status (at the presentation) after induction chemotherapy

Ref.	Author	Year	No. of patients	Remarks	
29	Som	1987	NA	(a) Ipsilateral node (s) ↓ the survival 58% (b) Bilateral nodes ↓ the survival 75% (c) Posterior triangle lymph nodes ↓ the survival 19%	
28	Olofsson *et al.*	1988	140	N0 > N + (survival)	
30	Recondo *et al.*	1988	28	non-N2c–N3 local control (55%)	N2c–N3 local control (21%)
31	Spaulding *et al.*	1988	49	N1 > local control (92%)	N2–3 local control (16%)

Table 4. Relationship between CR and site after induction chemotherapy

Ref.	Author	Year	No. of patients	Remarks
17	Hong *et al.*	1981	55	NS
18	Perry *et al.*	1981	64	NS
6	Al-Sarraf	1984	159	NS
8	NCI Contract Programme	1987	462	larynx > oral cavity pyr. sinus ($P < 0.001$)
23	Al-Sarraf *et al.*	1988	77	NS
16	Ildstad *et al.*	1988	542	Survival ↓ in tonsil ($P = 0.01$)
15	Pinnaro *et al.*	1988	152	↑ CR in oral cavity ($P = 0.04$)
32	Wolfansberger	1988	800	larynx > hypopharynx

Table 5. Performance status in relation to initial chemotherapy response and survival

Ref.	Author	Year	No. of patients	Remarks
33	Amer *et al.*	1979	164	PS ≥ 50 vs. PS ≤ 40, significant
18	Perry *et al.*	1981	64	NS (all patients > 50)
8	NCI Contract Program	1987	462	(a) NS for CT response (b) Significant (in patients > 90) for survival
15	Pinnaro *et al.*	1988	152	Significant
34	Cognetti *et al.*	1989	148	Significant 0–1 > 2 ($P = 0.001$)

Table 6. CR versus PR in relation to survival after neoadjuvant chemotherapy

Ref.	Author	Year	No. of patients	CR versus PR
35	Decker *et al.*	1983	35	CR > PR
36	Al-Kourainy	1987	191	CR > PR
37	Al-Sarraf	1987	216	CR > PR
38	Ervin *et al.*	1987	114	CR > PR (3 yr DFS 83% vs. 44%)
15	Pinnaro *et al.*	1988	152	CR > PR ($P = 0.0007$)
31	Spaulding *et al.*	1988	94	CR > PR (minimal follow-up 3.5 yr 5 yr DFS (61% vs. 35% all group)
34	Cognetti *et al.*	1989	148	CR > PR ($P = 0.0003$)

DFS = disease-free survival.

Table 7. Histopathological features, responses to chemotherapy and survival

Ref.	Author	Year	Remarks
39	Schuller *et al.*	1983	No correlation
40	Hong *et al.*	1984	No correlation
6	Al-Sarraf	1984	NS (159 patients)
41	Hill *et al.*	1986	No correlation
19	Price and Hill	1986	NS
20	Crissman *et al.*	1987	CR (114 patients) Non-keratinising (96%) vs. keratinising (65.5%) $P = 0.025$ Survival at 24 month Non-keratinising vs. keratinising ($P = 0.002$) C.R. > 2 mitotic figures (76%) vs. < 2 mitotic figures (46%) ($P = 0.02$)
14	Jacobs *et al.*	1987	No correlation
42	Abdel-Fattah *et al.*	1988	PD SCC = ↓ survival
43	Ensley *et al.*	1988	P.D. ↑ response to chemotherapy 36 months survival PD 18% – MD 38% WD 75%
44	Nielsen *et al.*	1988	No correlation
25	Crissman *et al.*	1984	mitosis ↑ = ↓ survival

PD = poorly differentiated, MD = moderately differentiated, WD = well differentiated.

(f) *Pathological parameters.* (i) *Differentiation.* This parameter has not been investigated as intensively as for other tumour types. For some, differentiated tumours carry a similar prognosis to undifferentiated tumours. In contrast, Crissman found a significant difference between keratinising non keratinising tumours [20, 25]. In his report, the difference was significant for response rate and for 2-year survival in favour of non-keratinising tumours. The mitotic index was also found to be significant. Other authors report a reonine difference in favour of well differentiated tumours (Table 7).

Cell kinetic parameters estimated by a ^{3}H-thymidine labelling index technique may be used to predict recurrence. At 30 months, the fast proliferating tumours have a high recurrence rate (76%) than slowly proliferating tumours (36.3%) [26].

(ii) *Flow cytometry parameters* are being evaluated. Table 8 shows the correlation between T stage, nodal status and ploidy. On balance, more advanced tumours are seen more often to be non-diploid. Several authors have focused on the correlation between abnormal DNA content and response to treatment in non-diploid tumours [27, 28]. If we consider the relationship between DNA content and local recurrence or survival, the results are conflicting, and an overall pattern has not emerged (Table 9).

Some other tumour parameters are known to influence the response to chemotherapy; these include quality of the tumour vascularisation. This parameter is now evaluable indirectly by assessing nodal density by CT scan. Cvitkovic *et al.* compared the density of the nodes and found that hypodensity (< 33% compared to muscle density) is associated with a high response rate (68% CR vs. 8% for density > 33%).

From all these parameters, it may be possible to derive a score for chemotherapy response, which may permit rational selection of patients for treatment. By this means we could then hope to demonstrate an increased survival by using chemotherapy in good risk patients.

Table 8. Relationship between abnormal DNA content (diploidy vs. non-diploidy) and T stage and nodal status

Ref.	Author	Year	No. of patients	T stage	N status
27	Guo *et al.*	1988	296	T3 + T4 ↑ with NDP	N+ ↑ with NDP
27	Nielsen *et al.*	1988	50	↑ T stage is not more with NDP	N+ is not more with NDP
45	Kokal *et al.*	1989	76	T3 + T4 ↑ with NDP	N+ and capsular invasion ↑ with NDP

NDP = non-diploid

Table 9. Relationship between abnormal DNA content (diploidy vs non diploidy) and local recurrence and survival

Ref.	Author	Year	No. of patients	Local recurrence	Survival
46	Chang *et al.*	1988	31	↑ with NDP	↓ with NDP
27	Guo *et al.*	1988	296	↑ with NDP	↓ with NDP
44	Nielsen *et al.*	1988	50	↓ with NDP	↑ with NDP
28	Olofsson *et al.*	1988	71	↑ with NDP in T1–T2 ↓ with NDP in T3–4	↓ with NDP in T1–2 ↑ with NDP with T3–4
45	Kokal *et al.*	1989	76	↑ with NDP in all stages	↓ with NDP in all stages

Table 10. % clinical CR in relation to the number of cycles administered

Ref.	Author	Year	No. of patients	No. of cycles	% CR
47	Al-Sarraf *et al*	1979	40	1	2.5%
48	Eliais *et al.*	1979	22	1	18%
49	Wittes *et al.*	1979	21	1	0%
50	Stell *et al.*	1983	86	1	3%
8	NCI Contract Program	1987	462	1	5%

Table 11. % clinical CR in relation to the number of cycles administered

Ref.	Author	Year	No. of patients	No. of cycles	% CR
51	Holoye *et al.*	1985	83	1–2	10%
52	Randolph *et al.*	1978	21	2	19%
53	Glick *et al.*	1980	29	2	0%
31	Spaulding *et al.*	1988	28	2	18%
17	Hong *et al.*	1981	55	2	20%
54	Kish *et al.*	1982	NA	2	19%

Table 12. % clinical CR in relation to the number of cycles administered

Ref.	Author	Year	No. of patients	No. of cycles	% CR
36	Al Kourainy	1987	191	2–3	39%
35	Decker *et al.*	1983	NA	3	54%
39	Schuller *et al.*	1984	146	3	20%
56	Haas *et al.*	1986	50	3	17%
57	Martin *et al.*	1986	60	3	7%
14	Jacobs *et al.*	1987	30	3	43%
58	Mazeron *et al.*	1989	118	3	7%
59	Demard *et al.*	1987	134	3	45.5%

Table 13. Cisplatin/5-FU dose-response relationship when increasing cisplatin dose

Ref.	Author	Year	Dose	CR	Overall response
35	Decker *et al.*	1983	Cisplatin 100 mg/m² over 5 days—5-FU 1000mg/m² 5 days	54%	93%
61	Kish *et al.*	1988	Cisplatin 150 mg/m² over 5 days—5-FU 1000mg/m² 5 days	45%	98%
59	Demard *et al.*	1987	Cisplatin 100 mg/m² D1 then 5-FU 1000 mg/m² D2–D6 all repeated 15 days	45.5%	86.6%

IMPROVING RESPONSE TO CHEMOTHERAPY

Number of cycles of chemotherapy

Tables 10, 11 and 12 show a clear relationship between the number of courses and the CR rate with an optimum number of 3 courses.

Dose response

Data from studies in which the doses of 5-FU and cisplatin have been varied (as single agent or in combination) are summarised in Tables 13, 14 and 15. No obvious dose response relationships are evident at these higher dose levels.

CHEMOPREVENTION OF SECOND MALIGNANCY

Since 13-cis-retinoic acid has been demonstrated to be active in premalignant lesions, this agent has been included in a randomised placebo-controlled trial for patients in complete

Table 14. Cisplatin/5-FU dose-response relationship when using cisplatin as a single agent with 2 dose schedules

Ref.	Author	Year	Dose	CR	Overall response
62	Veronesi *et al.*	1985	(1) Cisplatin 120 mg/m² for 2 cycles	1/31 (3%)	5/31 (16%)
			(2) Cisplatin 60 mg/m² for 2 cycles	0/28 (0%)	5/28 (17.8%)

Table 15. Cisplatin/5-FU dose-response relationship when increasing the 5-FU dose

Ref.	Author	Year	Dose	CR	Overall response
65	Greenberg	1987	Cisplatin 100 mg/m² over 5 days + 1500 mg 5-FU over 5 days	45%	100%

response after surgery and/or radiotherapy [60]. There is a significantly lower failure rate in the 13 CRA arm (31% versus 52%), median although follow-up is short at 29 months. The question of chemoprevention is being further evaluated in an EORTC protocol where N-acetyl-cystein or retinol palmitate or placebo are given to patients treated for laryngeal cancer; Tis, T1, T2, T3, oral cancer T1, T2 and for both larynx and oral cancer N1 (EORTC protocol Euroscan).

LYMPHOMAS

Overall 10–15% of head and neck tumours are recognised as lymphoma, usually non-Hodgkin lymphoma (NHL). Since there is no real difference in management between NHL presenting in the head and neck, and that presenting elsewhere, chemotherapy should be along similar lines.

UNDIFFERENTIATED CARCINOMA OF NASOPHARYNX (UNCT)

UNCT is a completely different tumour to squamous cell cancer, occurring in a different group of patients. Epidemiological studies point to the involvement of the Epstein–Barr virus (EBV) in its aetiology. Distant metastases are frequent at any stage including the apparently early stage of the disease. As the tumour is undifferentiated, it is known to be very radio- and chemosensitive. Bleomycin, anthracyclines and cisplatin are the most active drugs. Despite this high chemosensitivity, the role of induction chemotherapy or chemotherapy given in the adjuvant setting or both is still controversial.

ADENOID CYSTIC CARCINOMA (ACC)

ACC is usually a very slowly growing tumour producing a low rate of distant metastases. These lesions might be asymptomatic for a long period of time. Thus the activity of chemotherapy and its possible benefit for these patients is difficult to evaluate, particularly as the disease is uncommon. Only small series are available for scrutiny. In monochemotherapy, cisplatin and 5-FU achieve a response rate of more than 40%. Anthracyclines are nearly as effective. So far, the role of chemotherapy is not clearly defined in this disease.

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Controlling Emesis Related to Cancer Therapy

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Combinations of dopamine antagonists or high-dose metoclopramide with steroids can provide complete control of chemotherapy-related nausea and vomiting in up to 60–70% of patients undergoing high-dose cisplatin-based chemotherapy. High-dose metoclopramide probably acts as a 5-HT_3 receptor antagonist, but because of its dopamine-receptor antagonism it is the cause of extrapyramidal side-effects. These compounds, and the agents used in combination with them, tend to cause sedation, an undesirable effect in the outpatient setting. Specific 5-HT_3 receptor antagonists (ondansetron, granisetron, tropisetron) give a similar control of chemotherapy related nausea and vomiting, with minimum side-effects. These drugs can cause headaches and constipation and some have been related to transient liver enzyme abnormalities in cancer patients; however, disease and chemotherapy might also be the cause of the enzyme anomalies. Combinations of 5-HT_3 receptor antagonists with steroids may provide a very high degree of protection.
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INTRODUCTION

AFTER THE pioneering efforts of Moertel [1], cancer patients had to wait for a long time before any significant advance could help them with the most feared experience related to cancer chemotherapy, namely nausea and vomiting [2–4].

CLASSIC DRUGS

Corticosteroids

Used in many areas of medicine, sometimes with a rational basis related to their anti-inflammatory effect or in the treatment of specific deficiency states, corticosteroids have also a role in the control of cancer therapy related emesis [5]. Pilot studies of their probable antiemetic effect [6, 7] were rapidly followed by randomised evaluations, and their efficacy as sole antiemetics in patients treated with moderately emetogenic chemotherapy was proven in the early 1980s [8]. Investigators have not yet defined an optimal dose-schedule for the use of these compounds, whose antiemetic mechanism of action remains unknown, although it may be suggested that they act by modifying capillary permeability of the central nervous system [9]. Recent evidence indicates that steroids are efficacious in the animal models used for the study of other antiemetics, and thus support a mechanism unrelated to the general sense of well-being and possible placebo-effect that they may confer [10,11].

Metoclopramide, alizapride and neuroleptics

The most extensively studied agent is metoclopramide, which was proven to prevent high-dose cisplatin related nausea and vomiting [12]. Its use has been subject to several modifications, in logically conducted studies which have successively shown that it can be advantageously combined with steroids and a neuroleptic, to provide antiemetic protection for up to 60–70% of patients treated with high-dose cisplatin based chemotherapy [13].

It is generally accepted that patients younger than 35 years old will frequently experience extrapyramidal side-effects related

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