Low dose neoadjuvant chemotherapy in head and neck cancers : anti-tumour activity, prediction of radiotherapy response and influence on survival

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ABSTRACT

184 consecutive patients, all recently diagnosed and previously untreated, received a chemotherapy consisting of bleomycin (10 mg), etoposide (100 mg) and cisplatinum (15 mg) given as single course on days 1,3,5,15,17 and 19. There were 147 males and 37 females, aged 27-91 (mean 58). Oropharynx (68), oral cavity (37), larynx (35) and hypopharynx (25) were the predominant sites. Most tumours were locally advanced (27 T1, 55 T2, 51 T3, 51 T4) with frequent lymph nodes involvement (95 N0, 25 N1, 4 N2, 63 N3). Squamous cell carcinoma was present in 175 cases. A significant anti-tumour activity was obtained :

CHEMOTHERAPY	Patients	Tumour	Nodes
CR	11%	14%	6%
PR	59%	72%	52%
CR + PR	70%	86%	58%

Side-effects were minimal; no hyperhydration programm nor mannitol diuresis was used; chemotherapy was given on an ambulatory mode. Exclusive irradiation was delivered to full dose (TDF 103) in 148 cases with good tolerance of normal tissues. Chemotherapy response (C+) or non response (C-) influences tumour control after radiotherapy :

RADIOTHERAPY	Patients		Tumour		Nodes	
	C+	C-	C+	C-	C+	C-
Complete control	82%	39%	95%	67%	60%	33%

Short term effects on survival seem encouraging :

SURVIVAL	55 stage III	79 stage IV
2 years rate	60%	50%
3 years rate	50%	30%

Trends exist for a 10-15% benefit as compared to our own historical controls. Predictive neo-adjuvant chemotherapy might be of great value for treatment optimization and individualization.

KEYWORDS

Neo-adjuvant chemotherapy, head and neck cancers, bleomycin, etoposide, cisplatinum.

INTRODUCTION

A study is going on to assess the efficacy and the feasability of chemotherapy before planned radical irradiation or surgery in head and neck cancers with bad prognosis. The main purpose is to obtain a reduction of tumour volume in order to increase radiosensitivity, especially in hypoxic areas, and to ensure a better surgical resection. An effect on occult metastases already present at the time of diagnosis is also anticipated. Prior chemotherapy must not unduly delay the planned radical treatment nor add peculiar complications to irradiation or surgery. Side-effects should be minimal with a good patients compliance.

PATIENTS

184 consecutive patients were enrolled, all recently diagnosed and previously untreated. There were 147 males and 37 females, aged 27 to 91 (mean 58). Karnofsky index was higher than 70. The predominant sites of disease are detailed in Table 1 Staging referring to UICC TNM classification is given in Table 2.

SITES

Oropharynx	68	Tonsil	51
		Base of tongue	13
		Soft palate	4
Oral cavity	37	Floor of mouth	14
		Tongue	13
		Gingiva	6
		Cheek mucosa	3
		Hard palate	1
Larynx	35		
Hypopharynx	25		
Nasopharynx	7		
Nasal cavities	4		
Salivary glands	3		

Table 1.

TUMOUR STAGING

	UICC					AJC	
	N0	N1	N2	N3			
T1	17	4	0	6	27	I	17
T2	28	6	1	22	55	II	28
T3	22	6	1	22	51	III	56
T4	28	9	2	12	51	IV	83
	95	25	4	62			

All M0

Table 2.

Histology consisted of squamous cell carcinoma in 175 cases (90 well differentiated, 33 moderately differentiated, 31 poorly differentiated and 21 non other specified). There were 8 adenocarcinomas and 1 synovialosarcoma.

TREATEMENT POLICY

All stages of hypopharynx, nasopharynx and oropharynx cancers are treated by chemotherapy prior to exclusive radiotherapy. T3 N3 and T4 larynx receive the same association. Tumours of the oral cavity whatever T ans N are treated by chemotherapy, surgery and post-operative irradiation.

NEO-ADJUVANT CHEMOTHERAPY

A. Agents

A single course chemotherapy regimen associates bleomycin (10 mg), etoposide (100 mg) and cis-paltinum (15 mg) in a 3 hours IV perfusion of one litre normal saline. This low dose chemotherapy is given six times over a three weeks period on days 1,3,5 and 15,17,19. Ancillary support consists of anti-emetics given as needed. No hyperhydration nor forced diuresis was used. This treatment is carried out on an amulatory mode.

B. Response rate

The results are clinically assessed 8 days after the last injection. Response criterias are those in standard use : complete response (CR) in case of tumour dissepearance, partial response (PR) when the product of 2 diameters is reduced by more than 50%, minor response (MR) when the reduction is less than 50%, no response (NR) in case of stable disease or even tumour progression.

An overall response rate of 70% was obtained (CR + PR). As shown in Table 3, primary lesions proved more sensitive than lymph nodes.

T RESPONSE (175 TARGETS)	*N RESPONSE (82 TARGETS)*
CR = 14%	*CR = 6%*
PR = 72%	*PR = 52%*
CR + PR = 86%	*CR + PR = 58%*
MR = 11%	*MR = 32%*
NR = 3%	*NR = 10%*

Table 3.

The response rate differs according to tumour site (floor of mouth, tonsil and tongue tumours showing the maximum of sensitivity) and correlates with the target volume. On the contrary, histological differentiation seems to exert no influence (Table 4).

PARAMETERS OF RESPONSE

1. Tumour site	*T°*	*N°*	*GLOBAL°*
Tonsil	*98*	*70*	*78*
Larynx	*66*	*54*	*62*
Hypopharynx	*76*	*50*	*61*
Floor of mouth	*100*	*40*	*75*
Tongue	*92*	*25*	*75*
Base of tongue	*64*	*33*	*50*

° per cent major responses (CR + PR)

2. Target volume	*T1*	*T2*	*T3*	*T4*	*N1*	*N2*
% CR	*26*	*14*	*19*	*3*	*5*	*0*
% PR	*53*	*69*	*72*	*69*	*53*	*58*
% CR + PR	*79*	*83*	*91*	*72*	*58*	*58*

3. Histology	*T°*	*N°*
Well differentiated	*82*	*56*
Moderately differentiated	*83*	*47*
Poorly differentiated	*92*	*59*

° per cent major responses (CR + PR)

Table 4.

C. Side effects

The side effects remained acceptable without any life-threatening complications. 85% of patients experienced nausea (mild to severe) and 50% had vomiting. Digestive intolerance was maximal on days 1 and 15. A mild hematologic depression - leukopenia and thrombopenia - usually occured. Treatment had to be protracted in 4% of cases by doubling the time interval; etoposide dose was reduced by half in 8% of cases. No renal dysfunction was observed as measured by rise of serum levels of creatinine. No pulmonary side-effects were encountered but 2 transient bronchospasms occured at the time of injection. Alopecia has been noted in 20% of cases, more frequently among women. 2 patients experienced mild cutaneous effects from bleomycin.

RADICAL TREATMENT

The planned radical treatment consisted of exclusive radiotherapy (148 cases) or surgical resection followed by irradiation (22 cases). 14 non-respects of planning included patient refusals of treatment and cases where clinical deterioration prevented further treatment.
The radical treatment was always initiated without undue delay (mean interval of 15 days for radiotherapy and 18 days for surgery). Irradiation was always given to full dose (TDF 103) using a split-course modality. The local tolerance was unchanged as compared to historical controls treated in the same way. No cumulative toxic effects on normal tissues was observed. 92 patients were eligible for a further chemotherapy with monthly courses of high dose methotrexate (3 gm) and leucovorin rescue. The neo-adjuvant chemotherapy did not alter the tolerance to this long term maintenance treatment.

RESULTS

A. Anti-tumour activity

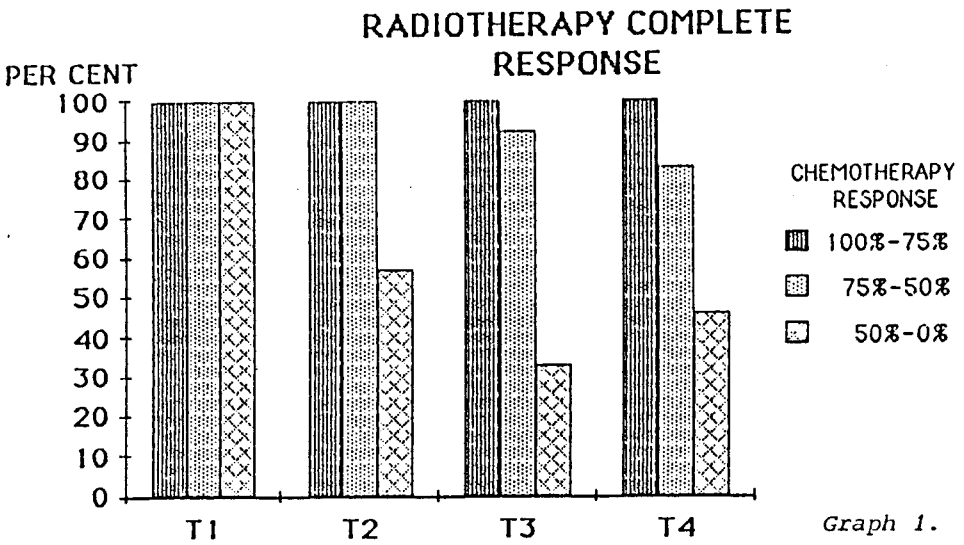
Early assessment indicates that high rates of tumour control were achieved after exclusive radiotherapy. Within one month after the end of irradiation, 88% of primary tumours had totally regressed and the complete regression rate of lymph nodes amounted to 54% (multiple nodes in the same patient being considered as a single target).

B. Prediction of radiotherapy response

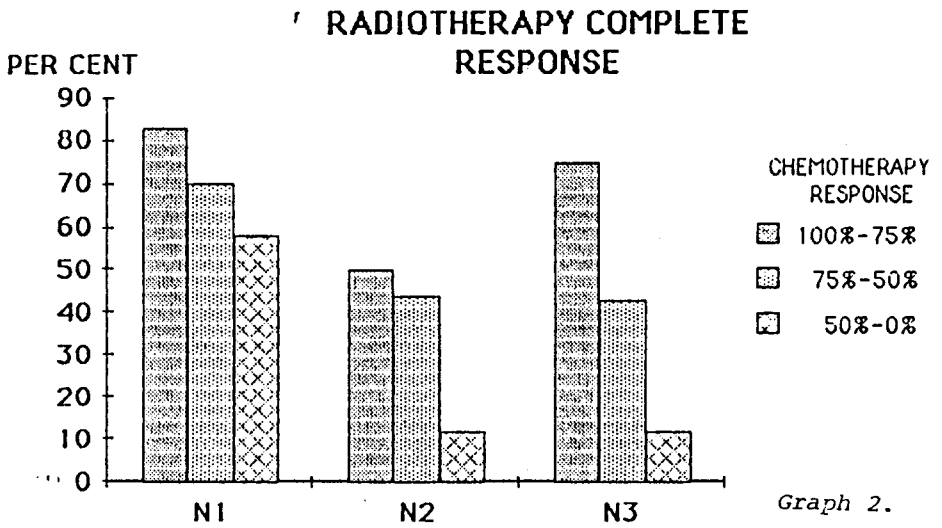
A clear-cut correlation exists between chemotherapy and radiotherapy responses. For primary tumours, 95% of complete regressions occur among chemotherapy good responders versus 67% among chemotherapy poor responders. The predictive value of chemotherapy is observed for all stages except for T1 where irradiation controls 100% of cases (graph 1). The same correlations are observed for nodes : 60% of complete regressions occur among chemotherapy good responders versus 33% among chemotherapy poor responders. Subdivision following N1, N2 and N3 shows that poor responders to chemotherapy have only 10% probability of being controlled (graph 2).

C. Influence on survival

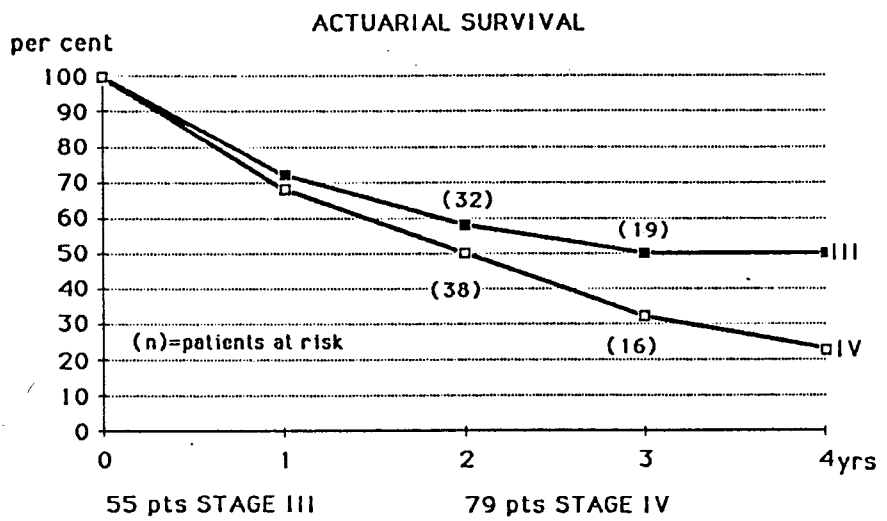
The long term benefit is still putative. Stage III patients survival is 57% at 2 years and 48% at 3 years with perhaps a plateau phase. 50% of stage IV patients are still alive at 2 years but only 31% at 3 years and the curve is still going down (graph 3). A comparison is on study with historical controls treated in the same way except for neo-adjuvant chemotherapy. Trends exist for a ten per cent possible benefit.
However more cases and time are needed.



Graph 1.



Graph 2.



Graph 3.

Résumé

184 patients consécutifs, tous diagnostiqués récemment et sans traitement antérieur ont reçu une chimiothérapie consistant en Bléomycine 10 mg, Vépéside 100 mg, Cis.Platyl 15 mg, donné en une perfusion aux jours 1,3,5, 15,17 et 19. Il y avait 147 hommes et 37 femmes, de 37 à 91 ans (moyenne : 58 ans). Il s'agissait d'oropharynx (68 cas), de la cavité buccale (37 cas), de larynx (35 cas), d'hypopharynx (25 cas), la plupart des tumeurs étaient localement avancées (27 T1, 55 T2, 51 T3, 51 T4) avec envahissement ganglionnaire fréquent (95 N0, 25 N1, 4 N2, 63 N3). Une histologie de cancer épidermoïde a été retrouvée dans 175 cas. Une activité significative anti-tumorale a été obtenue avec une rémission complète chez 11 % des malades avec des effets secondaires négligeables. Une rémission complète après radiothérapie a été observée chez 82 % des malades sensibles à la chimiothérapie et chez 39 % des malades qui étaient résistants. La survie à court terme est encourageante avec 60 % de survie à 2 ans, 50 % de survie à 3 ans pour 55 stades III, 50 % à 2 ans, 30 % de survie à 3 ans pour 79 stades IV.

Par rapport à nos propres contrôles historiques, le bénéfice est de 10 à 15 %.

La valeur prédictive de la chimiothérapie semble d'être de grande valeur pour l'opimisation et l'individualisation du traitement.