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Neo-adjuvant chemotherapy in head and neck cancers with low-dose combination of bleomycin, etoposide and cis-platinum

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128 patients were given a chemotherapy prior to planned irradiation or surgery. There were 98 males and 30 females , aged 27-91. The predominant sites were : oropharynx (48) , oral cavity (21) , larynx (29) and hypopharynx (14). Most tumours were locally advanced (20 T1 , 28 T2 , 51 T3 , 25 T4) with frequent lymph node involvement (65 N0 , 19 N1 , 3 N2 , 37 N3). Squamous cell carcinoma was present in 120 cases. The chemotherapy consisted of bleomycin (10 mg) , etoposide (100 mg) ans cis-platinum (15 mg) given on days 1 , 3 , 5 and 15 , 17 , 19. A response rate of 73% was obtained. Tumours regressed in 85% and nodes in 61%. Side-effects were minimal : 85% nausea , 50% vomiting , 10% mild hematologic depression , 20% alopecia. BVP chemotherapy was carried out on an ambulatory mode. Radical surgery was initiated without undue delay. In all cases , irradiation has been given to full dose with normal tolerance. Complete control was achieved in 89% of tumours and 58% of lymph nodes. Survival rates at 2 years of 35 stage III and 49 stage IV patients are respectively 68% and 46%. These promising results need to be confirmed on more cases with a longer follow-up period.

KEYWORDS

neo-adjuvant chemotherapy , head and neck cancers , bleomycin , etoposide , cis-platinum.

INTRODUCTION

A pilot study has been initiated 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.

PATIENTS

128 consecutive patients were enrolled , all recently diagnosed and previously untreated. There were 98 males and 30 females , aged 27 to 91 (mean 57). Karnofsky index was higher than 70. The predominant sites of disease are detailed in Table I. Staging referring to UICC TNM classification is given in Table II.

OROPHARYNX	48	TONSIL	36
		BASE OF TONGUE	11
		SOFT PALATE	1
ORAL CAVITY	21	FLOOR OF MOUTH	11
		TONGUE	11
		CHEEK MUCOSA	2
		GINGIVA	2
		HARD PALATE	1
LARYNX	29		
HYPOPHARYNX	14		
NASOPHARYNX	4		
NASAL CAVITIES	1		
SALIVARY GLANDS	3		

Table I

	N_0	N_1	N_2	N_3		
T_1	14	2	0	4	20	
T_2	16	5	0	7	28	
T_3	21	6	2	22	51	ALL M_0
T_4	14	6	1	4	25	
	65	19	3	37	124	

Table II

Histology consisted of squamous cell carcinoma in 122 cases (77 well differentiated , 21 moderately differentiated , 24 poorly differentiated). There were 5 adenocarcinomas and 1 synovialosarcoma.

TREATMENT POLICY

A 11 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 whichever T and 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-platinum (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 hyperhydratation programm nor mannitol diuresis was used. This treatment is carried out on an ambulatory 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 73% was obtained (CR + PR). As shown in Table III , primary lesions proved more sensitive than lymph nodes. The response rate was not influenced by histological differentiation nor tumour volume but differed according to tumour site.

T RESPONSE (123 TARGETS)

CR = 12%

PR = 73%

CR + PR = 85%

MR = 11%

NR = 4%

N RESPONSE (59 TARGETS)

CR = 7%

PR = 54%

CR + PR = 61%

MR = 32%

NR = 7%

RESPONSE RATE INDEPENDANT OF

- HISTOLOGICAL DIFFERENTIATION
- TUMOUR STAGE

17 CR AMONG 3 T_1 2 N_1

3 T_2 2 N_3

7 T_3

DEPENDANT OF

- TUMOUR-SITE

	T	N
TONSIL	100%	77%
LARYNX	65%	50%

Table III

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 cases by doubling the time interval ; etoposide dose was reduced by half in ten cases. No renal dysfunction was observed as mesured by 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 (100 cases) or surgical resection followed by irradiation (18 cases). 9 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 16 days). 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. 54 patients were eligible for a further chemotherapy with monthly courses of high dose methotrexate (3 gm) and leucovorin rescue. The induction chemotherapy did not alter the tolerance to this maintenance treatment.

RESULTS.

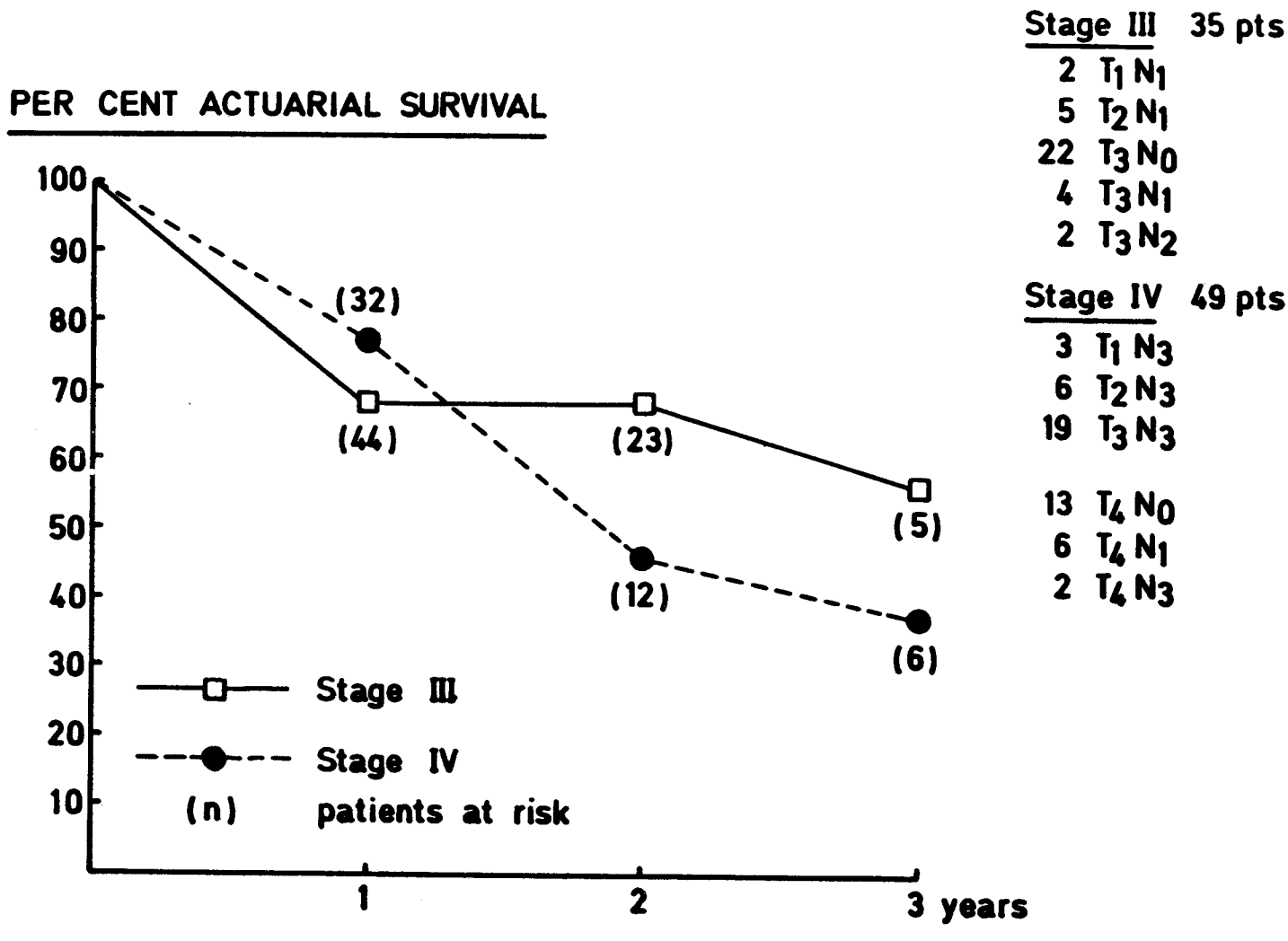
A. Tumour control.

Early assessment indicated that high rates of tumour control were achieved after exclusive radiotherapy. At the very end of irradiation , 77 primary tumours out of 87 had completely regressed (89%) and the complete regression rate of lymph nodes amounted to 26/45 (58%) (multiple nodes in the same patient being considered as only one target.

Owing to the small number of non-responders to chemotherapy , a correlation is difficult to establish up to now between chemotherapy and radiotherapy responses.

B. Survival.

The evaluation of a possible long-term benefit is still putative. The survival curves for 35 stage III (American Joint Comittee) patients and 49 stage IV patients are shown in Figure 1.
Rates at 2 years seem promising but more cases and time are needed. A randomized trial should be indicated.


PER CENT ACTUARIAL SURVIVAL
100
90
80
70
60
50
40
30
20
10
(32)
(44)
(23)
(5)
(12)
(6)
Stage III
Stage IV
(n) patients at risk
1
2
3 years
Stage III 35 pts
2 T1 N1
5 T2 N1
22 T3 N0
4 T3 N1
2 T3 N2
Stage IV 49 pts
3 T1 N3
6 T2 N3
19 T3 N3
13 T4 N0
6 T4 N1
2 T4 N3

CONCLUSIONS.

A combination of bleomycin , etoposide and cis-platinum at low doses has shown significant anti-tumour activity with minimal toxicity. This neo-adjuvant chemotherapy is suitable for outpatient treatment.

Irradiation and surgery are possible without delay and the tolerance is unchanged. A further chemotherapy is not precluded.

High rates of immediate tumour control are obtained after radiotherapy. More cases and time are needed to ascertain a positive effect on the long term prognosis.

Résumé

128 patients ont reçu une chimiothérapie préalable à une chirurgie et/ou une radiothérapie à visée curative. Le groupe comprenait 98 hommes et 30 femmes , âgés de 27 à 91 ans : il s'agissait de cas récemment diagnostiqués et n'ayant encore reçu aucun traitement. Les principaux sites anatomiques étaient : l'oropharynx (48) , la cavité buccale (21) , le larynx (29) et l'hypopharynx (14). La plupart des tumeurs se trouvaient à un stade avancé (20 T1 , 28 T2 , 51 T3 , 25 T4) avec envahissement ganglionnaire fréquent (68 N0 , 19 N1 , 3 N2 , 37 N3). Dans 120 cas , l'analyse histologique avait montré la présence d'un épithélioma épidermoïde.
La chimiothérapie associait la bléomycine (10 mg) , l'étoposide (100 mg) et le cis-platinum (15 mg) donnés à raison d'une seule cure aux jours 1 , 3 , 5 et 15 , 17 et 19. Un taux de réponses majeures de 73% a été obtenu. 85% des tumeurs primaires et 61% des adénopathies ont régressé de plus de la moitié en volume. Les effets secondaires furent minimes : 85% de nausées , 50% de vomissements , 10% de dépressions hématologiques modérées , 20% d'alopécies mais pas de toxicité rénale , pulmonaire ni cutanée. La chimiothérapie BVP a été pratiquée de façon ambulatoire , en administrant des anti-émétiques mais sans hyperhydratation ni diurèse forcée.
Une chirurgie radicale a pu être pratiquée sans retard et aucun effet néfaste n'a été observé sur les tissus sains du fait de la chimiothérapie préalable. Tous les cas ont pu recevoir une irradiation à dose complète (TDF 103) avec une bonne tolérance. Un contrôle complet a été obtenu pour 89% des tumeurs primaires et pour 58% des adénopathies. Les taux de survie à 2 ans pour 35 stades III et 49 stades IV sont respectivement de 68% et 46%. Ces résultats paraissent prometteurs mais nécessitent une confirmation sur un plus grand nombre de cas et un recul plus important.