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Review Paper

Chemotherapy in Head and Neck Cancer

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Chemotherapy has been used for many years as a palliative approach to advanced squamous cell carcinoma of the head and neck. Regimens employed have slowly evolved during this time, and the combination of cisplatin and 5-fluorouracil is still standard chemotherapy for such a tumour. However, clinical approaches to advanced squamous cell carcinoma of the head and neck are changing dramatically as physicians become increasingly familiar with multidisciplinary treatments. Integrating chemotherapy and radiotherapy, neo-adjuvant or adjuvant treatments and organ preservation are stimulating fields of investigation involving chemotherapy which definitely warrant further investigation.

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INTRODUCTION

SQUAMOUS CELL carcinoma of the head and neck (SCC-HN) accounts for almost 3% of all cancers detected annually in western countries. Despite it is being a relatively rare disease, its dramatic impact on patient quality of life and the poor treatment results make SCC-HN a major clinical problem. Although some chemotherapeutic regimens may produce up to 50% complete response rates in previously untreated patients [1, 2], the disease may still be considered a chemotherapy-resistant tumour. While many drugs play a minor role in clinical practice [3], no more than three to four drugs are active in single-agent therapy (Table 1). Finally, chemotherapy alone has no impact on survival, even if it may control symptoms in many patients for months or, rarely, for years.

What we can and cannot currently achieve with chemotherapy is reviewed here, and what we can reasonably expect during the forthcoming years is discussed.

Table 1. Single-agent chemotherapy

Chemotherapeutic agent	Response rate (%)
Methotrexate	31
Cisplatin	28
Carboplatin	22
Bleomycin	21
5-Fluorouracil	15

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CHEMOTHERAPY AS PALLIATIVE TREATMENT: THE HISTORICAL BACKGROUND

Palliation is the historic role for chemotherapy in the management of SCC-HN. For many years, methotrexate-based regimens were the only reasonable palliative treatment for relapsed head and neck cancer patients. Expected response rates never exceeded 30%, with only occasional complete responses. Al-Sarraf first employed the combination of cisplatin and 5-fluorouracil [4] obtaining, in particular, a limited but definite complete response rate of 15–20%. The EORTC has also suggested an effective regimen based on the combination of cisplatin, methotrexate, bleomicin and vincristine (CABO) [5]. However, although CABO has shown activity comparable to the Al-Sarraf regimen, it is less frequently used than cisplatin/5-fluorouracil in clinical practice.

Regardless of the treatment employed, patients reaching complete response generally have a longer (and better) survival than do partial responders, but most of these also, have a temporary complete relief of their symptoms. Therefore, another 15–20% of relapsed patients temporarily benefit from palliative chemotherapy. We may thus conclude that at least one third of patients treated with palliative intentions have a substantial improvement. Unfortunately, the duration of clinical response, even if the best regimens are employed, still only extends for some months. It is reasonable to expect a median duration of 3–6 months for partial responses and 6–9 months for complete responses. There is only a minor, if any, impact on survival. The simple observation that responders have a longer survival compared to non-responders in most clinical trials is *per se* not sufficient to conclude that this is because of chemotherapy. It could simply mean that patients with the best survival more frequently respond to chemotherapy [6]. Chemotherapeutic regimens for squamous cell carcinoma of the head and neck generally produce only mild toxicity, and this does not compromise clinical results.

Table 2. Randomised trials comparing mono- to polychemotherapy in recurrent or metastatic SCC-HN

Author	Chemotherapy	No. of patients	OS	TTP	Survival
Jacobs *et al.* [11]	CDDP+FU		32%		
	CDDP	249	17%	$P<0.03$	N.S.
	FU		13%		
Forastiere *et al.* [12]	CDDP+FU		32%		
	CBDCA+FU	277	21%	N.S.	N.S.
	MTX		10%		

OS, overall survival; TTP, time to progression; CDDP, cisplatin; FU, 5-fluorouracil; CBDCA, carboplatin; MTX, methotrexate; N.S. = not significant.

However, the role of well-trained oncology staff (medical oncologists and oncology nurses) to reduce the incidence and severity of such side-effects is crucial.

Second-line palliative chemotherapy is less likely to provide benefits. Generally, we cannot anticipate a positive response in patients not responding to an effective first-line therapy [7]. Moreover, efficacy of methotrexate is reduced when given to patients already treated with cisplatin [8]. In our experience, patients achieving a complete response to first-line chemotherapy with cisplatin and 5-fluorouracil have about a 30% chance of responding further to the same chemotherapy at relapse (data not shown). Unfortunately, the high probability of neurological toxicity at cumulative platinum dosages of 500 mg/m^2 or more [9] limits the usefulness of this agent. The same regimens active in locally relapsed SCC-HN also show activity in metastatic disease; lung metastases seems to be more responsive than do other deposits at other sites [10].

Although single-agent chemotherapy has now almost become obsolete because of the lower response rate and the shorter time to progression compared to multidrug chemotherapy, there are no reported significant differences in survival between single-agent and multi-agent chemotherapy [11, 12] (Table 2). Indeed, methotrexate alone may still be considered an effective alternative in elderly patients or whenever performance status limits the use of more aggressive regimens. Moreover, it seems that previous methotrexate treatment does not reduce platinum/5-fluorouracil activity [8].

To date, the Al-Sarraf regimen is, for most clinical oncologists, the standard first-line treatment for relapsed SCC-HN. However, the CABO regimen is probably as active as platinum/5-fluorouracil and boasts two main advantages: it is easier to administer on an out-patient basis and, because of the lower dosage of platinum employed, has less neurological toxicity. On the other hand, CABO has important drawbacks compared to the Al-Sarraf regimen. CABO includes both vincristine, inactive in this tumour and dangerous particularly in elderly patients (ileus, paresthesias), and bleomycin which is contraindicated in a large number of head and neck cancer patients [13], and whose true value against this disease is controversial [14]. Finally, although CABO is easily administered in an out-patient setting, it requires the patient to visit the hospital every week, leaving few days for rest. For those patients receiving chemotherapy in a palliative setting, this may be a major disadvantage.

CHEMOTHERAPY AS PART OF A FIRST-LINE MULTIDISCIPLINARY APPROACH

Two facts are important. First, chemotherapy alone is unable to cure any SCC-HN and, second, surgery and/or radiation therapy have allowed marginal improvements over the last two decades. There are thus solid reasons for investigating new approaches, such as chemotherapy combined with surgery and/or radiation.

Two different approaches have indeed been investigated. Firstly, adjuvant or neoadjuvant chemotherapy, which entails the sequential administration of chemotherapy and radiotherapy and/or surgery, and secondly, alternating or simultaneous chemotherapy and radiation, followed or preceded, if necessary, by surgery.

There is a profound conceptual difference between the two approaches: neoadjuvant or adjuvant chemotherapy at best reflects the sum of the efficacies of the single modalities while, on the contrary, alternating or simultaneous chemotherapy and radiotherapy leads to a close temporal integration of the two modalities with the purpose of influencing the biological mechanisms through which each modality determines its cytotoxic effects, with the results possibly being synergistic.

Neoadjuvant or adjuvant chemotherapy

Many authors have attempted to test adjuvant chemotherapy after radical local treatment. Unfortunately, to avoid compromising results of local therapies, drugs were initially delivered after surgery and/or radiation, thus starting chemotherapy under the worst conditions of performance status because of ablative surgery and/or extensive radiotherapy. Moreover, the use of some drugs after radiation results in increased toxicity. Both of these considerations account for the high rate of patients who have not completed adjuvant chemotherapy in these early trials (Table 3) [15–20]. More recent studies of adjuvant chemotherapy strive to insert chemotherapy between surgery and radiation to improve patient compliance [20]. There are no definitive results from this approach as yet. Nonetheless, the development of simultaneous chemotherapy and radiotherapy in an adjuvant setting, which allows administering both treatments without delay [21], may represent a significant advance towards overcoming the abovementioned limits of sequential adjuvant chemotherapy and radiotherapy. An interesting randomised trial designed by Cognetti in Rome, presently in progress, is comparing standard radiotherapy to a simultaneous chemo-radiotherapy, both in an adjuvant setting.

The abovementioned difficulties in pursuing classic adjuvant chemotherapy have prompted the development of neo-adjuvant chemotherapy. During the 1980s, a number of randomised trials were performed to compare combined local therapies alone to these plus neoadjuvant chemotherapy (Table 4) [16, 17, 21–28] but no definitive benefits in survival were seen.

Table 3. Randomised trials of adjuvant chemotherapy in head and neck cancer

Author	No. of patients	CT	DFS (%) Control		DFS (%) CT	Survival (%) Control		Survival (%) CT	
Rentschler [15]	60	MTX	59	N.S.	66	55	N.S.	55	
H&NCP [16]	462	CDDP	55	N.S.	64	35	N.S.	45	27% of patients at least three cycles of CT Significant reduction in distant metastases
Taylor [17]	95	MTX, CDDP, ADM	37	N.S.	50	41	N.S.	41	Poor compliance
Szpirglas [18]	95	MTX, BLM	47	N.S.	52	58	N.S.	58	
Ervin [19]	46	CDDP, BLM, MTX	61	$P<0.05$	84	—		—	10/26 patients received three cycles of CT
Laramore [20]	442	CDDP, 5FU	38	N.S.	46	44	N.S.	46	Trend for high-risk patients. Significant reduction in distant metastases

CT, Chemotherapy; DFS, disease-free survival; MTX, methotrexate; CDDP, cisplatin; ADM, doxorubicin; BLM, bleomycin; N.S. not significant.

Table 4. Randomised trials of neoadjuvant chemotherapy vs. radiotherapy alone in head and neck cancer

Author	No. of patients	Chemotherapy	Results
Fazekas [21]	638	MTX	No difference
Arcangeli [22]	142	MTX i.a.	Improved survival (oral cavity only)
H&NCP [16]	443	CDDP, BLM	No difference
Taylor [17]	95	MTX	No difference
Kun [23]	83	CTX, BLM, MTX, 5-FU	Advantage in survival for control arm
Stell [24]	86	VCR, MTX, 5-FU, Hy, 6MP, CTX	Advantage in survival for control arm
Shuller [25]	158	CDDP, VCR, MTX, BLM	No difference
Jaulerry [26]	100	CDDP, BLM, VND, Mit-C	No difference Significant reduction in distant metastases
	108	CDDP, 5-FU, VND	with chemotherapy
Paccagnella [27]	237	CDDP, 5-FU	No difference Significant difference in survival for inoperable patients Significant reduction in distant metastases with chemotherapy
Richard [28]	222	VCR, BLM i.a.	Improved survival (oral cavity only)

MTX, methotrexate; CDDP, cisplatin; BLM, bleomycin; CTX, cyclophosphamide; 5-FU, 5-fluorouracil; VCR, vincristine; Hy, hydroxyurea; 6MP, 6-mercaptopurine; VND, vindesine; Mit-C, mytomicin C; i.a., intra-arterial.

Nevertheless, the experiences accrued with neoadjuvant chemotherapy allowed the development of an impressive field in head and neck oncology: organ preservation. This topic will be analysed in the appropriate section of this paper.

Alternating or simultaneous chemotherapy and radiotherapy

As mentioned above, this approach is biologically different from the sequential administration of radiotherapy and chemotherapy. The main consequence is a different clinical target. Sequential therapy strives for spatial cooperation, with chemotherapy to eradicate distant metastases and radiotherapy to eradicate loco-regional disease. Integrated chemo-radiotherapy on the other hand entails synergistic activity between the two modalities in the irradiated areas. Since most head and neck cancers recur locally, and loco-regional disease is the usual cause of death, this type of local cooperation is more important than spatial cooperation. To accomplish this goal, both treatments must be effective *per se* as otherwise, the role of chemotherapy is limited to a sort of radiosensibilisation, as has been tested in many trials [29–35] (Table 5). In this case, however, single-agent chemotherapy is used, sometimes at lower dosages than those usually employed in clinical practice. Similar trials are still in progress, but most multidisciplinary teams are currently devoted to investigating the integration of chemotherapy and radiotherapy as reported above. The

Table 5. Randomised trials of concomitant single-agent chemotherapy and radiotherapy vs. radiotherapy in head and neck cancer

Author	No. of patients	Chemotherapy	Results
Vermund [29]	222	BLM	No difference Increased local toxicity
Eschwege [30]	199	BLM	No difference Increased local toxicity
Shanta and Krishnamurthy [31]	157	BLM	Improved survival and local control (oral cavity only) Increased local toxicity
Fu [32]	104	BLM	Improved local control Trend to improved survival Increased local toxicity
Ansfield [33]	134	5-FU	Improved survival
Lo [34]	151	5-FU	Improved survival and local control Increased local toxicity
Sanchiz [35]	859	5-FU	Improved survival to standard RT* No difference with hyperfractionated RT*

BLM, bleomycin; 5-FU, 5-fluorouracil; RT, radiotherapy. *Data reported only for complete responders.

pioneering work of Taylor *et al.* [36] opened this field early in the 1980s, although clinical data alternating VBM (vinblastine, bleomycin, methotrexate) and split-course radiotherapy had been published earlier by O'Connor *et al.* [37].

Single-agent chemotherapy and radiotherapy. The first large randomised trial comparing the efficacy of radiotherapy with that of a combination of cytotoxic and radiation treatment was conducted more than 20 years ago [33]. Since then, many other randomised trials have been performed with single-agent chemotherapy and radiotherapy.

Overall, two drugs have received the most attention: bleomycin and 5-fluorouracil (Table 5).

Trials employing bleomycin have generally given negative results, while 5-fluorouracil achieved better results, including improved response rates and survival. Reviewing the trials reported in Table 5, we can argue that toxicity has been the determining factor for these observed differences in results. Indeed, bleomycin has frequently been discontinued due to severe local reactions, while 5-fluorouracil has been much better tolerated. It is important to stress that 5-fluorouracil has been given as a bolus i.v. injection, thus preserving the mucosae from a cross-toxicity between the drug and radiation.

Multiagent chemotherapy and radiotherapy. More recently, multiagent chemotherapy has been associated with radiotherapy in clinical trials. Although there is still a wont for randomised trials comparing this combined approach to radiotherapy alone, the introduction of polychemotherapy has led to impressive objective response rates in up to 90% and more, including a large proportion of complete responses [38].

Taylor *et al.* has recently updated the clinical experience with cisplatin and 5-fluorouracil given concomitantly to radiotherapy in an alternate week schedule [39]. Complete response rates are in the range reported by similar trials, but freedom from disease progression (close to 60% at 2 years) and survival (62% at 2 years) appear substantially improved.

Unfortunately, this treatment is hampered by a substantial increase of side-effects as shown by a randomised trial comparing Taylor's scheduling to neoadjuvant chemotherapy followed by radiotherapy [40]. At a median follow-up of 30 months, this trial failed to show significant benefits in survival, but had a substantial excess of deaths from disease-unrelated causes in the concomitant arm. A longer follow-up is mandatory to adequately evaluate the study.

Vokes *et al.* employed the combination of 5-fluorouracil infusion and hydroxyurea plus radiotherapy every other week in the treatment of advanced or relapsed SCC-HN [41]. Although use of this drug combination is unusual in SCC-HN, both experimental and clinical data support this choice because of the evidence of a positive interaction between the drugs [42] and between the drugs and radiation therapy [43, 44]. The activity of the combined chemo-radiotherapy resulted in 70% complete responses and 30% partial responses among patients not previously treated. More importantly, this study showed that synchronous chemotherapy and radiotherapy also plays a role in patients with relapsed disease, including those who received radiotherapy for treatment of primary tumour. The Institute Gustave Roussy employed the same scheduling in patients with inoperable recurrent SCC-HN and preliminary results seem to confirm Vokes' report [45].

Dobrowsky *et al.* [46] added mitomicin-C and 5-fluorouracil to pre-operative radiotherapy and histopathologically evaluated the treatment. 23 of 41 evaluable patients reached pathological complete response (56%). The relatively early stages of tumours in these patients (only 6 T4 and 1 N3) might explain such a positive result. Nevertheless it was achieved with only 5000 cGy and a single course of chemotherapy. Wendt *et al.* [47] combined chemotherapy (cisplatin, low-dose 5-fluorouracil infusion and leucovorin) with accelerated radiotherapy. 62 patients, all but 4 with stage IV tumours, entered the trial. 48 patients reached a complete response (77%) and 11 a partial response (18%). The 2-year survival was 52%, but 5% of the patients died from haemorrhage during treatment.

In conclusion, concomitant multi-drug chemotherapy and radiotherapy seem to be an effective treatment. Unfortunately, despite major changes in radiotherapy planning, toxicity still remains a limiting factor for such an approach. Cross toxicity

Table 6. Alternating chemo-radiotherapy—phase II studies

Author	Schedule	No. of patients	OR (CR) %	Grade III–IV mucosal toxicity (%)
Rosso [49]	4 VBM/20 Gy × 3	45	89 (58)	24
Merlano [50]	4 CDDP, FU bolus/ 20 Gy × 3	34	88 (47)	6
Corvò [51]	3 CDDP, FU bolus/ 32 Gy × 2 b.i.d.	16	80 (60)	44

OR, objective responses; CR, complete responses; VBM, vinblastine, bleomycin, methotrexate; CDDP, cisplatin; FU, 5-fluorouracil; b.i.d., twice fraction per day.

Table 7. Alternating chemo-radiotherapy—phase III studies

Author	Study design	No. of patients	OR (CR) (%)	PFS (%)	Survival (%)	Grade III–IV mucositis (%)
Merlano [52]	4VBM/20 Gy × 3		65 (33)	12 (4 years)	22 (4 years)	29
	vs.	116		$P<0.02$	$P<0.02$	$P<0.0004$
	4 VBM→65–70 Gy		52 (14)	4 (4 years)	10 (4 years)	4
Merlano [53]	4 PF/20 Gy × 3		71 (43)	25 (3 years)	41 (3 years)	19
	vs.	157	$P<0.04$	$P<0.01$	$P<0.05$	N.S.
	65–70 Gy		65 (22)	7 (3 years)	23 (3 years)	18

OR, objective responses; CR, complete responses; PFS, progression-free survival; VBM, vinblastine, bleomycin, methotrexate; PF, cisplatin and 5-fluorouracil; N.S., not significant.

between the drugs employed and radiotherapy, and the lack of rest between chemotherapy and radiotherapy, can account for increased side-effects.

Alternating chemotherapy and radiotherapy

To reconcile the needs for both the early administration of chemotherapy and radiotherapy and a better tolerance of the combined approach, we developed a clinical programme based on the alternating delivery of both agents.

Since the first phase II study was undertaken in 1979 [48] to verify data previously reported by O'Connor [37], other uncontrolled trials have been performed (Table 6) [49, 50] to test different chemotherapy scheduling or radiotherapy fractionations. These provide the basis for two large randomised trials conducted between 1983 and 1990 (Table 7).

The first randomised cooperative trial compared two different methods of administering chemotherapy during a multidisciplinary approach to advanced SCC-HN. The study was activated in 1983 and enrolled 116 patients with stage III-IV, unresectable, previously untreated, SCC-HN. Patients were randomly assigned to receive four cycles of VBM as neoadjuvant chemotherapy followed by radical radiotherapy or to the same chemotherapy alternating with three courses of radiotherapy. Identical chemotherapy (drugs, dosages, scheduling and interval) was given in both treatment arms to reduce variables.

The alternating approach was significantly more successful in terms of complete response, progression-free survival and overall survival [51, 52]. The largest difference observed between the two treatments was seen in patients with the worse prognostic factors. In particular, patients with very advanced disease (T4 and/or N3) treated with the alternating regimen had a 4-year survival of 21 vs. 4% of those treated with neoadjuvant chemotherapy. This result is surprising since only 1–2% of long-term survivors have been reported in this sub-group of patients [14]. This finding is further confirmed by the survival rate seen in the neoadjuvant arm.

The combined approach, however, produced a significant increase in mucosal toxicity, most likely due to a negative interaction between radiotherapy and methotrexate.

The second randomised trial started in 1987, and sought to compare alternating chemotherapy and radiotherapy (four courses of cisplatin and 5-fluorouracil, and three split-courses of radiotherapy) to radiation alone. In this study, standard radiotherapy (the control arm) was given with radical intent up to 70 Gy/35 fractions, five fractions/week. Elegibility criteria were the same as in the previous phase III trial. 157 patients were enrolled. All patients had stage III (39 patients) or IV (118 patients), unresectable SCC-HN. There were 104 patients with very advanced disease (T4 and/or N3), thus allowing allocation of 52 patients per arm. Accrual was stopped on 31 December 1990, and statistical analysis performed in 1992 showed a significant improvement in survival for patients treated with alternating chemotherapy and radiotherapy [53]. Moreover, analysis showed that complete responses were twice as frequent in the alternating arm, while local relapses in complete responders were twice as frequent in the 'radiotherapy-alone' arm. Distant failures were similar, regardless of the treatment arm. In conclusion, this trial has shown that chemotherapy and radiotherapy help local control, and that improving local control may result in significantly better survival.

ORGAN PRESERVATION

Studies on neoadjuvant chemotherapy have shown that those tumours responding to drugs have a very high probability of responding to radiation as well. Jacobs *et al.* [54] was the first to recognise the clinical relevance of this observation. She tested the hypothesis that, because of this behaviour, it is possible to identify those patients who can avoid laryngectomy

in favour of definitive radiotherapy. Following her preliminary data, the U.S. Veterans Administration [55] performed a large multicentric randomised trial which showed that patients responding to neoadjuvant chemotherapy can avoid total laryngectomy. Treatment with radiotherapy leaving surgery as salvage treatment had no negative impact on survival. As this approach warrants further investigation, other trials are presently in progress by the EORTC Head and Neck Oncology Group and by the Rush Medical College of Chicago in other primary sites such as the hypopharynx.

However, because neoadjuvant chemotherapy has no impact on survival, the need for aggressive drug scheduling as well as for multiple courses to identify patients responsive to chemotherapy is questionable. Further studies must identify less intensive regimens and shorter treatments able to achieve the same goal.

CONCLUSIONS

Frequently, head and neck cancer develops into a mutilating disease which gives rise to major problems. Chemotherapy can adequately palliate symptoms in about 35–40% of the patients, but it is unclear whether it can also improve survival. It is reasonable to believe that improvement in survival will result from the development of new regimens able to substantially improve the complete response rate.

Chemotherapy as part of a front-line multidisciplinary treatment for advanced SCC-HN is a stimulating field of investigation and data available from 20 years of clinical studies suggest that neo-adjuvant or adjuvant chemotherapy has a minor role in improving survival of advanced disease. The incidence of distant metastases has been reduced but not local relapses, which are most often the cause of patient death.

The integration of chemotherapy and radiotherapy seems to offer a better chance of survival. At present, however, few studies have shown any significant improvement in survival compared to standard radiotherapy, although many have documented improvement in progression-free survival and/or objective response rate. In conclusion, there should be more studies of integrated chemo-radiotherapy. Unfortunately, the pursuit of serious clinical investigations into this matter is hampered by both the optimism and pessimism (each largely unjustified) of the international scientific community. The optimists, starting from insufficient data, tend to hold the superiority of chemo-radiotherapy over radiotherapy alone as being undisputable. As a consequence, studies designed by some of these authors lack the appropriate control arm and thus exclusively compare two experimental treatments. The pessimists tend to underestimate the value of available clinical data and this reduces the chances of further investigations. This approach is unjustified in the light of the absence of clearly negative results and the availability of positive data in some well designed and conducted clinical studies. We need further studies employing the appropriate control arm, which means, for inoperable disease, radiation therapy alone.

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