B-ENT, 2016, **12**, 29-32

Induction chemotherapy before surgery for unresectable head and neck cancer

H. Schmaltz[1], *C. Borel*[2], *S. Ciftci*[1], *C. Takeda-Raguin*[3], *C. Debry*[1], *P. Schultz*[1] *and A. Dupret-Bories*[4]

[1]Department of Otorhinolaryngology, CHU Hautepierre, Strasbourg, France; [2]Department of medical oncology, Centre Paul Strauss, France; [3]Geriatric Department, Hôpital Universitaire de Strasbourg, Strasbourg, France; [4]Department of Otorhinolaryngology, Institut Universitaire du Cancer, Toulouse, France

Key-words. Head and neck cancer; induction chemotherapy; surgery; unresectable tumour

Abstract. *Induction chemotherapy before surgery for unresectable head and neck cancer. Objective*: To preoperatively reduce tumour size in patients with locally advanced and/or non-resectable squamous cell carcinoma with induction chemotherapy in order to achieve surgical excision with clear margins and preserve quality of life.
Methodology: In this study, 16 patients with locally advanced and/or non-resectable squamous cell carcinoma underwent induction chemotherapy with docetaxel, cisplatin, and 5-fluorouricil or paclitaxel, carboplatin, and cetuximab.
Results: Over 80% of patients responded to induction chemotherapy. Histological examination of the 14 surgical specimens showed a total absence of residual cancer cells in 37.5% of cases.
Conclusion: Concurrent radiation and chemotherapy is the standard treatment for locally advanced head and neck squamous cell carcinoma; however, induction chemotherapy may be beneficial in select patients.

Introduction

Concurrent radiation and chemotherapy (CRC) is the gold standard for treatment of locally advanced head and neck squamous cell carcinoma (HNSCC).[1] A minority of these patients can undergo adequate surgical resection, and the outcomes are poor with respect to survival and organ preservation.[2]

Few studies have investigated the benefit of induction chemotherapy (IC) before surgery to reduce the size of the tumour and improve the rate of successful resections and, ultimately, lead to better outcomes.[3,4] In this study, several patients with oral and pharyngolaryngeal carcinomas with low potential surgical curability were treated with IC to enable resection of the tumour with negative margins and preserve the patient's quality of life. Patients were treated with either docetaxel, cisplatin, and 5-fluorouracil (TPF) or paclitaxel, carboplatin, and cetuximab (PCC). The superiority of TPF to cisplatin plus 5-fluorouracil (PF) is undisputed, although TPF is also associated with significant toxicity.[5,6,7]

Case series

We present a retrospective analysis of all patients with oral or pharyngeal squamous cell carcinoma and low potential for surgical curability who received IC before surgery at our centre between May 2011 and July 2014. The management of all patients was decided in the multidisciplinary head and neck clinic at our centre. The study was approved by the Centre Paul Strauss Research Ethics Committee. Inoperable patients with predicted mutilating surgery or with tumours that were technically unresectable, had a high risk of incomplete surgical resection predicted by an experienced surgeon, high risk of micrometastasis assessed as advanced nodal status of N2b or more, thrombosis of the internal jugular vein, and major scalability were selected.

Patients received 3 cycles of TPF (docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1, and 5-FU 750 mg/m^2/day from days 1 to 4) every 3 weeks with systematic granulocyte colony stimulating factor support or 8 cycles of PCC (paclitaxel 80 mg/m^2, carboplatin area under the curve 2, and cetuximab 250 mg/m^2 on day 1) weekly.

The choice of regimen was decided based on the patients' performance status and creatinine clearance level. After 2 cycles of TPF or 8 cycles of PCC, patients were re-evaluated in the multidisciplinary clinic. Response was assessed clinically by the surgeons and radiologically according to the RECIST 1.1 criteria.[8] TNM status was determined before IC and after surgery, and survival rates were recorded.

The analysis was based on 16 patients aged 35 to 60 years. Original tumour sites were the oral cavity (N=6), oropharynx (N=7), piriform sinus (N=1), and metastatic lymphadenopathy of unknown primary (N=2). The tumour was classified as T3 or T4 in 93% of patients, and nodal status greater than or equal to N2b was present in 75% of patients. Thirteen patients received TPF and 5 PCC. Two patients receiving TPF experienced severe renal insufficiency and subendocardial ischemia, respectively, that required interrupting the treatment. Both patients were switched to treatment with PCC.

The response rate after IC was 80% according to computed tomography evaluation and 86.7% on the histological examination (3 complete responses [CR], 10 partial responses [PR], 1 stable disease, and 2 progressive disease).

Fourteen patients (87.8%) had sufficient reduction in their tumour size to undergo surgical resection.

Surgery depended on the initial tumour location (tumour resection with margins of at least 1 cm on the residual tumour, 2 cm for the hypopharynx), and functional or radical bilateral neck dissection (local or free flap). The piriform sinus tumour, which initially invaded the oropharynx and the entire tongue base, was resected using a total circular pharyngolaryngectomy and was rebuilt with a forearm free flap. Two patients were deemed unresectable after IC and treated with CRC, i.e. 70 Gy in 2-Gy fractions with weekly cisplatin or cetuximab.

The tumour status (before and after IC and surgery) and disease-free survival (DFS) data are presented in Table 1. The human papilloma virus (HPV) status of patients with oropharyngeal cancers was unknown.

R0 resection was possible in 85.7% of the patients who received surgery. The postoperative pathological examinations of 5 patients found no residual tumours (35.7%). The examination of one patient found tumour residue and a second intraepithelial neoplasia.

Seven patients were treated with postoperative radiotherapy (66 Gy) and 7 with CRC due to capsular rupture (n=4), incomplete surgical resection (n=2), and/or an immediate local recurrence (n=2). Median follow-up was 22.3 (range, 11-41) months after the first chemotherapy, and 18.5 months (8-37) after surgery. The overall survival rate is 87.5% to date, and 62.5% of patients (n=10) are disease free. The median DFS has not yet been reached. The outcome was unfavourable in 6 cases; 2 patients treated with TPF showed progressive disease and 1 patient had a PR but remained inoperable. There were 2 recurrences after surgery and CRC, both in patients treated with TPF. One patient had stable disease (ypT4N2bR1) and one had a partial response (T1N2b). One other recurrence occurred after surgery (n=1), the patient refused CRC. The median time to progression was 6.5 (range, 4-13) months.

Discussion

The 5 year-survival of patients with locoregionally advanced HNSCC is only 40% (10-30% for patients with stage IVa-b). Locoregional failure is the predominant cause of recurrence.[9] Currently, there are three options for patients with locoregionally advanced disease; (1) surgery with a high risk of R1 resection and/or high morbidity followed by CRC, (2) CRC alone, and (3) IC followed by CRC or surgery (widely accepted for laryngeal cancers).

The Decide and Paradigm phase III trials failed to prove that TPF before CRC was superior to CRC alone.[10] Recently, positive results were reported by the Gruppo di Studio sui Tumori della Testa e del Collo at the American Society of Clinical Oncology, i.e. sequential treatment with TPF and CRC was significantly superior to CRC alone in terms of survival.[11] Few cohorts of patients with HNSCC receiving IC prior to surgery have been reported. Patil *et al.* reported a study in which 721 cases of oral HNSCC were treated with IC. Of these patients, 310 (43%) had sufficient reduction in tumour size to undergo surgical resection.[3] Median estimated overall survival was 19.6 months for patients who underwent surgical resection and 8.16 months for patients who did not receive surgery. Zhong *et al.* recently showed no benefit of 2 cycles of TPF before surgery in a randomized trial enrolling 256 patients, but concluded that patients with favourable pathologic responses had improved outcomes.[4]

In our study, 14 of 16 patients underwent surgical resection. The response rate was over 80%, and seems to be underestimated by computed tomography evaluation compared to histological examination. Two patients who achieved a partial response after IC have had recurrences. No patient with a complete response has had a recurrence. This is in contrast to the outcomes of patients who

Table 1
TNM status before and after induction chemotherapy and surgery

Patient	cTNM	ypTNM	DFS (months)	OS (months)
#1	cT4N2b	ypT0N1	36	36
#2	cT4N2b	ypT4N0	22	22
#3	cT4N2b	NA	6	33 *
#4	cT4N3	ypT1N2c	27	27
#5	cT4N1	ypT0N0	23	23
#6	cT4N2b	ypT4N2b	7	18
#7	cTxN3	ypTxN2a	34	34
#8	cT4N0	ypT4N0	4	21
#9	cTxN3	ypTxN2a	18	18
#10	cT4N1	ypT4N1	41	41
#11	cT4N2c	y*pT0N0*	15	15
#12	*cT2N2c*	*ypT1N2b*	13	14
#13	cT4N2c	ypT0N0	11	11
#14	cT3N2b	ypT2N0	12	16
#15	cT4N2b	NA	5	15*
#16	cT4N2b	ypT0N0	12	12

*Deceased.
NA: not applicable; DFS: disease free survival; OS: overall survival.

had stable or progressive disease after IC. The initial response to IC seems to be a major prognostic criterion. Good responders should be identified quickly to avoid additional toxicity from TPF. Indications and patient selection must be strict, preferably including young subjects with a preserved general state, which is difficult in this context. Criteria predictive of response are not yet defined, but there are numerous potential factors (HPV status, biomarkers, PET-CT, and others).[12]

Five patients received PCC. This protocol compares favourably with TPF in the literature. Baumann and Kies reported response rates of 97% and 96% after 6 cycles of PCC.[13,14] PCC may cause fewer cardiac effects because of the absence of 5-fluorouracil, fewer renal effects due to less toxicity with carboplatin, and fewer haematological adverse events (5-19% rate of febrile neutropenia III-IV versus 23% with TPF).[11,13-15] This raises the question of cetuximab's value in IC. A team at MD Anderson is currently conducting a randomized phase II trial comparing PCC to cetuximab-TPF in order to determine the best induction protocol prior to CRC.

Intraepithelial neoplasia was identified distant to the residual tumour in one of our cases. It is possible that, centrifugal tumour regression did not achieve and chemotherapy may leave residual cancer cells in the peripheral tumour. This raises the question of whether surgical margins should match the initial tumour volume. If so, this may undermine the use of IC prior to surgery with the intent of avoiding mutilating surgery.

Conclusion

IC led to some patients with initially inoperable LAHNSCC becoming operable, making it a promising alternative to CRC. Criteria predictive of a response to IC will be essential to define in the future in order to select good responders and avoid unnecessary toxicity and therapeutic delay. The PCC protocol may be an interesting alternative to TPF, but requires further study.

References

1. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. 2000;355(9208):949-955.
2. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med*. 1993;328(3):184-194.

3. Patil VM, Prabhash K, Noronha V, Joshi A, Muddu V, Dhumal S, Arya S, Juvekar S, Chaturvedi P, Chaukar D, Pai P, Kane S, Patil A, Agarwal JP Ghosh-Lashkar S, Dcruz A. Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers. *Oral Oncol*. 2014;50(10):1000-1004.
4. Zhong LP, Zhang CP, Ren GX, Guo W, William WN Jr, Hong CS, Sun J, Zhu HG, Tu WY, Li J, Cai YL, Yin QM, Wang LZ, Wang ZH, Hu YJ, Ji T, Yang WJ, Ye WM, Li J, He Y, Wang YA, Xu LQ, Zhuang Z, Lee JJ, Myers JN, Zhang ZY. Long-term results of a randomized phase III trial of TPF induction chemotherapy followed by surgery and radiation in locally advanced oral squamous cell carcinoma. *Oncotarget*. 2015;6(21):18707-18714.
5. Hitt R, López-Pousa A, Martínez-Trufero J, Escrig V, Carles J, Rizo A, Isla D, Vega E, Marti JL, Lobo F, Pastor P, Valenti V, Belon J, Sanchez MA, Chaib C, Pallares C, Anton A, Cervantes A, Paz-Ares L, Cortés-Funes H. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol*. 2005;23(34):8636-8645.
6. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Raez LE, Cohen RB, Spaulding M, Tishler RB, Roth B, Viroglio RdC, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas D, Norris CM, Haddad RI. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357(17):1705-1715.
7. Vermorken JB, Remenar E, Van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Betka J, Preiss JH, Van Den Weyngaert D, Awada A, Cupissol D, Kienzer HR, Rey A, Desaunois I, Bernier J, Lefebvre JL. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*. 2007;357(17):1695-1704.
8. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
9. Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. *Nat Clin Pract*. 2007;4(3):156-171.
10. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, Clark J, Sarlis N, Lorch J, Beiler JJ, Limaye S, Riley S, Posner M. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(3):257-264.
11. Ghi MG, Paccagnella A, Ferrari D, Foa P, Rocca MC, Verri E, Morelli F, Azzarello G, D'Ambrosio C, Cruciani G, Guaraldi M, Massa E, Rossetto C, Bonetti A, Siena S, Minotti V, Koussis H, Pieri G, Baggio V, Floriani I. Concomitant chemoradiation (CRT) or cetuximab/RT (CET/RT) versus induction Docetaxel/Cisplatin/5-Fluorouracil (TPF) followed by CRT or CET/RT in patients with Locally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN). A randomized phase III factorial study (NCT01086826). *J Clin Oncol*. 2014;32 (suppl; abstr 6004).
12. Van Limbergen EJ, Dok R, Laenen A, Hauben E, Van den Weyngaert D, Voordeckers M, De Neve W, Duprez F, Nuyts S. HPV-related oropharyngeal cancers in Flanders (Belgium): a multicenter study. *B-ENT*. 2014;10(1):7-14.
13. Bauman J, Langer C, Quon H, Algazy K, Lin A, Desai A, Mutale F, Weiss J. Induction chemotherapy with cetuximab, carboplatin and paclitaxel for the treatment of locally advanced squamous cell carcinoma of the head and neck. *Exp Ther Med*. 2013;5(4):1247-1253.
14. Kies MS, Holsinger FC, Lee JJ, William WN, Glisson BS, Lin HY, Lewin JS, Ginsberg LE, Gillaspy KA, Massarelli E, Byers L, Lippman SM, Hong WK, El-Naggar AK, Garden AS, Papadimitrakopoulou V. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. *J Clin Oncol*. 2010;28(1):8-14.
15. Wanebo HJ, Lee J, Burtness BA, Ridge JA, Ghebremichael M, Spencer SA, Psyrri D, Pectasides E, Rimm D, Rosen FR, Hancock MR, Tolba KA, Forastiere AA. Induction cetuximab, paclitaxel, and carboplatin followed by chemoradiation with cetuximab, paclitaxel, and carboplatin for stage III/IV head and neck squamous cancer: a phase II ECOG-ACRIN trial (E2303). *Ann Oncol*. 2014;25(10): 2036-2041.

H. Schmaltz
Department of Otorhinolaryngology
CHU Hautepierre
67200 Strasbourg, France
E-mail: helene.schmaltz@chru-strasbourg.fr

A. Dupret-Bories
Department of Otorhinolaryngology
Institut Universitaire du Cancer
31059 Toulouse Cedex 9, France
E-mail: Dupret-Bories.Agnes@iuct-oncopole.fr