original article

Annals of Oncology 21: 1515–1522, 2010
doi:10.1093/annonc/mdp573
Published online 23 December 2009

Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study

A. Paccagnella[1]*, M. G. Ghi[1], L. Loreggian[2], A. Buffoli[3], H. Koussis[4], C. A. Mione[5], A. Bonetti[6], F. Campostrini[7], G. Gardani[8], A. Ardizzoia[9], D. Dondi[10], M. Guaraldi[11], R. Cavallo[12], L. Tomio[13] & A. Gava[14] for the Gruppo di Studio Tumori della Testa e del Collo XRP 6976 F/2501 Study

[1]Department of Medical Oncology, Venezia; [2]Department of Radiotherapy, Istituto Oncologico Veneto, Istituto di Ricerca e Cura a Carattere Scientifico, Padova; [3]Department of Radiotherapy, Azienda Ospedaliera Universitaria, Udine; [4]Department of Medical Oncology, Istituto Oncologico Veneto, IRCCS, Padova; [5]Department of Radiotherapy, Ospedale SS. Giovanni e Paolo, Venezia; Departments of [6]Medical Oncology and [7]Radiotherapy, Ospedale Mater Salutis, Legnago; Departments of [8]Radiotherapy and [9]Medical Oncology, S. Gerardo Hospital, Monza; [10]Sanofi-Aventis, Milano; [11]Department of Medical Oncology, S. Orsola-Malpighi Hospital, Bologna; [12]Department of Medical Oncology, P. Cosma Hospital, Camposampiero, Padova; [13]Department of Radiotherapy, S. Chiara Hospital, Trento and [14]Department of Radiotherapy, Ospedale Ca' Foncello, Treviso, Italy

Received 5 June 2009; revised 31 August 2009 & 15 October 2009; accepted 11 November 2009

Background: Concomitant chemoradiotherapy (CT/RT) is the standard treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN). We evaluated the efficacy of induction docetaxel (Taxotere), cisplatin, and 5-fluorouracil (TPF) before CT/RT versus CT/RT alone.

Patients and methods: Patients with stage III–IVM0 SCCHN, Eastern Cooperative Oncology Group performance status of zero to one, were randomly assigned to receive CT/RT alone (arm A: two cycles of cisplatin 20 mg/m^2, days1–4, plus 5-fluorouracil 800 mg/m^2/day 96 h continuous infusion, during weeks 1 and 6 of radiotherapy) or three cycles of TPF (arm B: docetaxel 75 mg/m^2 and cisplatin 80 mg/m^2, day 1, and 5-fluorouracil 800 mg/m^2/day 96 h continuous infusion, every 3 weeks) followed by the same CT/RT. The primary end point was the rate of radiologic complete response (CR) at 6–8 weeks after the end of CT/RT.

Results: A total of 101 patients were randomly allocated to the study (51 arm A; 50 arm B). CR rates were 21.2% (arm A) versus 50% (arm B). Median progression-free survival and overall survival were, respectively, 19.7 and 33.3 months (arm A) and 30.4 and 39.6 months (arm B). Hematologic and non-hematologic toxic effects during CT/RT were similar in the two arms.

Conclusion: Induction TPF followed by CT/RT was associated with higher radiologic CR in patients with locally advanced SCCHN with no negative impact on CT/RT feasibility.

Key words: concomitant chemoradiotherapy, head and neck cancer, induction chemotherapy

introduction

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of newly diagnosed cancers in adults and >500 000 new cases annually are predicted worldwide [1]. Standard treatment of resectable, stage III–IVM0 disease is surgery with or without adjuvant radiotherapy plus concomitant chemotherapy [1–4]. Unfortunately, >50% of patients with SCCHN present with locoregionally advanced disease technically unresectable or with low surgical curability. Phase III studies and the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) have shown that concomitant chemoradiotherapy (CT/RT) is optimal treatment of unresectable disease [5].

Although induction chemotherapy is frequently used in clinical practice and has role in organ preservation and in reducing distant metastases [6–8], its ability to prolong survival has not yet been demonstrated. Three phase III studies comparing two different induction chemotherapy regimens [cisplatin and 5-fluorouracil (PF) with or without a taxane] followed by either radiotherapy alone or radiotherapy plus chemotherapy have shown that adding a taxane to PF improves response rate, time to progression (TTP), and overall survival (OS) compared with PF [9–11].

Correspondence to: Dr A. Paccagnella, Department of Medical Oncology, Ospedale dell'Angelo, Via Paccagnella 11, Mestre, 30100 Venezia, Italy. Tel: +39-041-9658320; Fax: +39-041-9658326; E-mail: adriano.paccagnella@ulss12.ve.it

We designed the current phase II randomized trial to assess the radiologic complete response (CR) rate at the end of treatment in patients receiving either CT/RT alone or three cycles of induction docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by the same CT/RT. A secondary objective was to determine the feasibility, on the basis of efficacy and acceptable toxicity of TPF induction, of conducting a phase III trial with OS as the primary end point.

patients and methods

study design

This was an open-label, randomized, phase II study conducted at 18 Italian centers. Patients aged ≥18 years were eligible if they had histologically/cytologically proven stage III–IVM0 unresectable SCCHN of the oral cavity, oropharynx, or hypopharynx (larynx carcinomas were excluded because many are resectable at an advanced stage); one or more measurable lesion; Eastern Cooperative Oncology Group performance status (PS) of zero to one; adequate hematologic, hepatic, and renal function; life expectancy ≥6 months; no prior chemotherapy, radiotherapy, or surgery; no peripheral neuropathy or altered hearing greater than or equal to grade 2 and weight loss ≤20% in 3 months preceding the study. Inoperability criteria were technical unresectability (tumor fixation/invasion to either base of the skull, cervical vertebrae, nasopharynx, or fixed lymph nodes), low surgical curability (T3–T4, N2–N3 excluding T1 N2) as assessed by an experienced surgeon, and organ preservation.

All patients provided written informed consent. The protocol was approved by the ethics committee of the participating centers and the study was conducted in accordance with the Declaration of Helsinki. Registration and randomization were carried out centrally by phone or fax. Stratification was by T stage (T1–T2 versus T3–T4), N stage (N0–N1 versus N2–N3), and primary site (oral cavity/oropharynx versus hypopharynx).

treatment plan

Patients were randomly assigned to receive either CT/RT alone (arm A) or induction TPF followed by CT/RT (arm B). The CT/RT regimen consisted of standard fractionated radiotherapy of 70 Gy for the primary tumor (2 Gy/day, 5 days/week for 7 weeks) and a radiotherapy regimen of ≥60 Gy for the neck (2 Gy/day, 5 days/week for 5 weeks). For N2–N3 patients who were candidates for neck dissection, a minimum of 50 Gy for the neck was planned but most received 60 Gy. The CT/RT chemotherapy was cisplatin 20 mg/m^2/day (30 min i.v. infusion, from day 1 to 4) and 5-fluorouracil 800 mg/m^2/day (96 h continuous i.v. infusion) administered during weeks 1 and 6 of radiotherapy.

In arm B, induction TPF consisted of docetaxel (Taxotere; Sanofi-Aventis, Paris, France) 75 mg/m^2 (1-h i.v. infusion, day 1) followed by cisplatin 80 mg/m^2 (30-min i.v. infusion, day 1) and 5-fluorouracil 800 mg/m^2/day (96 h continuous i.v. infusion, starting after the cisplatin infusion). Cycles were repeated every 3 weeks to a maximum of three cycles. Antibiotic prophylaxis (oral ciprofloxacin 500 mg twice daily, days 5–15) was administered after each cycle. Patients received the same CT/RT regimen as in arm A, 3–5 weeks after the end of induction chemotherapy.

All patients were given adequate hydration and antiemetics (5-HT3 antagonists and dexamethasone). Prophylactic granulocyte colony-stimulating factor (G-CSF) was not allowed, but G-CSF was given to patients who experienced grade 4 neutropenia [absolute neutrophil count (ANC) <0.5 × 10^9/l lasting >7 days], febrile neutropenia, or delayed ANC recovery. Enteral support (feeding tube, percutaneous endoscopic gastrostomy) was considered before starting CT/RT.

A reduction or delay in chemotherapy dose was recommended if patients had an ANC <1500/μl, a platelet count <100 000/μl, and/or grade 2–4 non-hematologic toxic effects before starting chemotherapy. For a delay in TPF induction cycle >2 weeks, patients received immediate CT/RT.

evaluations

Staging was by the International Union Against Cancer 1997 tumor–node–metastasis classification [12]. Before study entry, all patients underwent a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the head and neck, chest X-ray and/or lung CT scan, abdominal ultrasound or liver CT scan for liver abnormalities, and brain and bone scans in the presence of specific symptoms.

Pathologic confirmation of radiologic CR at the primary site was carried out under anesthesia 8–12 weeks after the end of CT/RT. Neck dissection was planned for stage N2–N3 patients who achieved a pathologically confirmed CR at the primary site and a radiologic CR at the neck. Surgery was considered for radiological/clinical residual disease after CT/RT at one or both sites.

Radiologic head and neck examinations were carried out after induction TPF (arm B), 6–8 weeks after ending concomitant CT/RT (all patients), then every 6 months until progression. Patients were followed every 3 months for the first 2 years after completion of CT/RT and then every 6 months until progression or death.

end points

The primary end point was the radiologic CR rate evaluated 6–8 weeks after the completion of CT/RT. Secondary end points included overall response rate (ORR) [CR + partial response (PR)], duration of response, progression-free survival (PFS), OS, and feasibility. Duration of response was calculated from the date of first documented response to first documented disease progression. PFS was calculated from the date of randomization up to the date of first progression, second primary malignancy, or death from any cause. Patients not progressing and alive at the time of the analysis were censored at the last disease assessment date. OS was measured from the date of randomization until death. At the time of analysis, patients who were not reported as having died were censored at the date they were last known to be alive.

Responses were assessed by CT or MRI scans according to RECIST [13] and reviewed by an internal committee (radiologist, radiation oncologist, and medical oncologist) blinded to treatment assignment. Toxicity was assessed using National Cancer Institute of Canada—Clinical Trials Group expanded common toxicity criteria [14]. Late reactions to radiotherapy were graded by the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer late radiation morbidity criteria [15].

statistical analysis

The primary objective of the trial was to rank the two treatment arms according to the Simon approach [16], having as primary end point the CR rate. On the basis of this method, assuming the smallest CR rate of 30%, with 43 assessable patients per arm, there was a 90% probability of selecting the superior treatment by an absolute difference of 15% (i.e. the treatment with a true CR rate of 45%). Taking into account a rate of 10% of not assessable patients, a total of 96 patients had to be enrolled. Assessable for response patients were considered those meeting eligibility criteria, having received treatment assigned at randomization, with all baseline lesions reassessed at least once by the same method as used at baseline. Analyses of PFS and OS were carried out on the intent-to-treat population. Survival curves were described using Kaplan–Meier method and compared by log-rank test. Response rate were compared by means of the chi-square test. Results are presented as point estimates and 95% confidence intervals (CIs).

Since the goal of the study was to select the best regimen, the study was not powered for a formal comparison between the two arms. Therefore, all the comparisons made had only explorative purposes.

Analyses were carried out using SAS Software, version 9.1 (SAS Institute, Cary, NC).

results

patient characteristics

Overall, 101 patients were randomly allocated to the study from January 2003 to January 2006, with 51 assigned to CT/RT (arm A) and 50 to induction TPF followed by CT/RT (arm B). One patient (arm A) was subsequently deemed ineligible (Figure 1). Although technically resectable, two patients (CT/RT arm) were included for an organ preservation program as per protocol. Baseline characteristics were balanced, except a greater proportion of women and patients with PS of zero in arm A (Table 1).

activity

After induction TPF, the radiologic ORR was 69.5% (95% CI 49.2% to 77.1%) and the CR was 6.5% in the 46 assessable patients. Five patients (10.8%) progressed during TPF and were treated according to the corresponding center's practice. Following CT/RT, the radiologic CR rate was 21.3% (95% CI 10.7% to 35.7%) in arm A and 50% (95% CI 34.9% to 65.1%) in arm B indicating a better activity for arm B. The *P* value of the comparison between the two arms was equal to 0.004. Corresponding PR rates were 61.7% and 28.2% (Table 2).

Surgery for radiological/clinical residual disease was carried out in twice the number of patients in arm A (Figure 2). In arm A, 21 of the 47 assessable patients (44.6%) received surgery after chemoradiation. In 18 of 21 patients (85.7%), surgery was carried out due to residual disease after chemoradiation (16 patients with neck residual disease and 2 patients with residual disease both on the neck and primary site). In 3 of 21 additional patients (14%) initial stage N2–N3, the prophylactic neck dissection was carried out. In arm B, surgery was carried out in 17 of the 46 assessable patients (37%). In 9 of 17 patients (53%) received surgery due to residual disease after chemoradiation (5 patients with neck residual disease and 4 patients with residual disease both on the neck and primary site). In 8 of 17 additional patients (47%) initial stage N2–N3, the prophylactic neck dissection was carried out.

Radiologic CR rates evaluated 8 months after treatment of nonoperated patients (planned neck dissection or salvage surgery) were 40% (10 of 25 patients) in arm A and 57.1% (16 of 28 patients) in arm B. In arm A, five patients maintained a CR, five shifted from PR to CR, and two progressed after an initial CR. In arm B, 13 patients maintained CR, 3 shifted from PR to CR, and 1 progressed after an initial CR.

Median duration of ORR (CR + PR) was 29.7 months in arm A and 30.4 months in arm B.

efficacy

After a median follow-up of 42 months, 32 patients (62.7%) in arm A and 26 patients (52.0%) in arm B progressed or died; median PFS was 19.7 and 30.4 months, respectively (Figure 3A), with 44.7% and 55.6% of patients remaining progression free at 2 years. Median OS was 33.3 months in arm A and 39.6 months in arm B (Figure 3B), with 1- and 2-year survival rates of 77.6% and 57.1% in arm A and 86.0% and 61.0% in arm B, respectively.

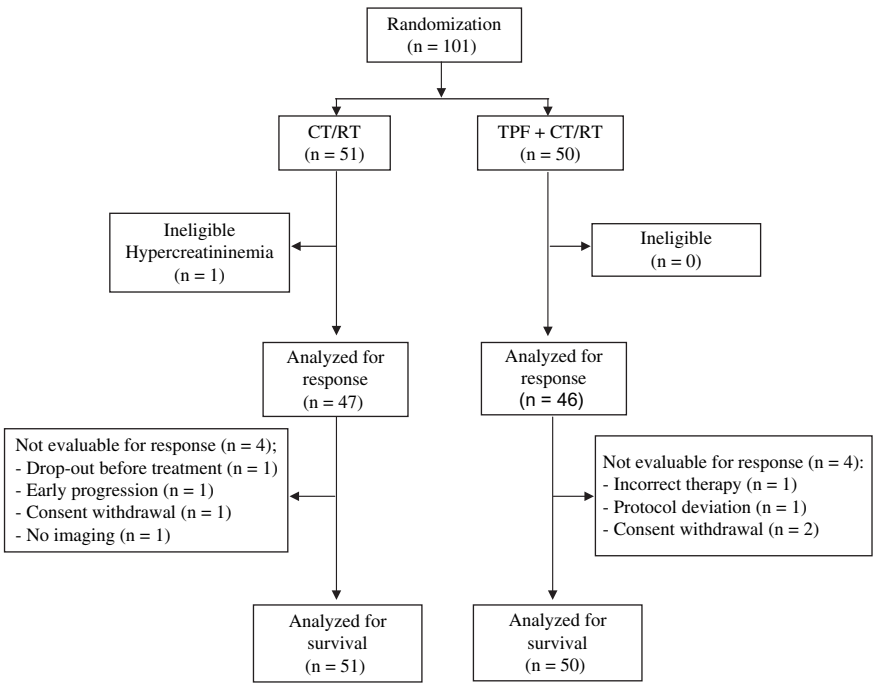

Figure 1. Patient flow.

adverse events

The rate of early death (within 30 days following treatment) in arm A was 9.8% (five patients). Among five causes of death, three were not treatment related: one cardiac disease, one bilateral pulmonitis (probably ab ingestis), and one gastric perforation. One was unknown and one was treatment related (infection in patient with hematologic toxicity). There were no early deaths in arm B.

During induction TPF, the most common grade 3–4 hematologic toxicity was neutropenia (52%; 26 of 44 assessable patients), with 8% ($n = 4$) experiencing febrile neutropenia. The rate of grade 3–4 anemia and thrombocytopenia was 2.0%. Grade 3–4 non-hematologic toxic effects occurring in >2% of patients were alopecia (18%), stomatitis/mucositis (6.0%), and nausea (4.3%).

Grade 3–4 hematologic toxic effects during CT/RT were not clinically relevant (Table 3). The most relevant non-hematologic toxic effects (mucositis/stomatitis, skin toxicity, and dysphagia) were not higher with TPF induction.

The median radiation dose, the median duration of CT/RT, and radiotherapy interruption rates were similar (Table 4). Overall, >90% of patients received two planned cycles of concomitant PF. In arm A, four patients (8%) received only one cycle of PF during radiotherapy ($n = 2$ disease progression; $n = 2$ toxicity). Two patients never started CT/RT (Figure 1). In three patients, cisplatin dose intensity was reduced by ~6%, with no 5-fluorouracil does reductions.

In arm B, 96% of patients ($n = 47$) received three planned cycles TPF induction and 4% ($n = 2$) received two cycles. The TPF dose intensities (mg/m^2/week) were 23.9 for docetaxel, 25.4 for cisplatin, and 101 for 5-fluorouracil. During concomitant treatment, three patients (7%) received only one cycle of PF during radiotherapy ($n = 1$ disease progression; $n = 2$ toxicity). In two patients, the cisplatin dose was reduced to 4.6%, with no 5-fluorouracil dose reductions. Seven patients never received CT/RT ($n = 5$, progression after TPF; $n = 1$, physician decision; and $n = 1$, consent withdrawn after induction CT).

Table 1. Characteristics of the patients

Characteristic	CT/RT (arm A) ($N = 51$)	TPF + CT/RT (arm B) ($N = 50$)
Eligible patients, *n*	50	50
Median age, years (range)	60 (40–80)	58 (36–75)
Male/female, *n*	38/13	46/4
ECOG PS, *n* (%)		
0	44 (86.2)	39 (78.0)
1	7 (13.8)	11 (22.0)
Anatomic site, *n* (%)		
Oral cavity/oropharynx	10/26 (70.6)	8/27 (70.0)
Hypopharynx	15 (29.4)	15 (30.0)
Clinical stage, *n* (%)		
III	9 (17.6)	8 (16.0)
IV	42 (82.4)	42 (84.0)
Reason for inoperability		
Technical unresectability	43 (84.3)	37 (74.0)
Low surgical curability	6 (11.8)	13 (26.0)
Organ preservation	2 (3.9)	0
Stage of primary tumor, *n* (%)		
T2	7 (14)	6 (12)
T3	22 (43)	21 (42)
T4	22 (43)	23 (46)
Nodal stage, *n* (%)		
N0	6 (12)	6 (12)
N1	11 (21)	12 (24)
N2	30 (58)	28 (56)
N3	4 (8)	4 (8)

CT/RT, concomitant chemoradiotherapy; TPF, docetaxel, cisplatin plus 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

discussion

Randomized trials evaluating the effectiveness of induction chemotherapy before locoregional therapy in SCCHN have not provided definitive outcomes due to suboptimal patient numbers, heterogeneous populations, and inactive chemotherapy regimens. Updated findings from the MACH-NC have shown a small nonsignificant OS advantage for induction chemotherapy followed by radiotherapy (2% at 2 and 5 years) over radiotherapy alone; however, when the analysis was limited to PF induction, OS was improved by 5.4% at 5 years ($P = 0.05$) [5, 17]. Only two positive phase III trials of induction chemotherapy have been published to date: the Gruppo di Studio sui Tumori della Testa e del Collo, which showed a survival benefit for patients who were considered ineligible for resection [18, 19] and the Groupe d'Etude des Tumeurs de la Tête et du Cou, which was limited to oropharynx cancer [20].

Thus, the benefit of induction chemotherapy in clinical practice compared with the present standard CT/RT is unclear. Two recent phase III randomized trials have demonstrated the

Table 2. Response rate 6–8 weeks after the end of CT/RT in assessable patients

Response	CT/RT (arm A) ($N = 47$), *n* (%)	TPF + CT/RT (arm B) ($N = 46$), *n* (%)	*P* value
Complete response (95% CI)	10 (21.3) (10.7% to 35.7%)	23 (50.0) (34.9% to 65.1%)	0.004
Partial response	29 (61.7)	13 (28.2)	
Stable disease	0	1 (2.2)	
Progressive disease	8 (17.0)	9 (19.5)	
Overall response rate	39 (83.0)	36 (78.2)	

CT/RT, concomitant chemoradiotherapy; TPF, docetaxel, cisplatin plus 5-fluorouracil; CI, confidence interval.

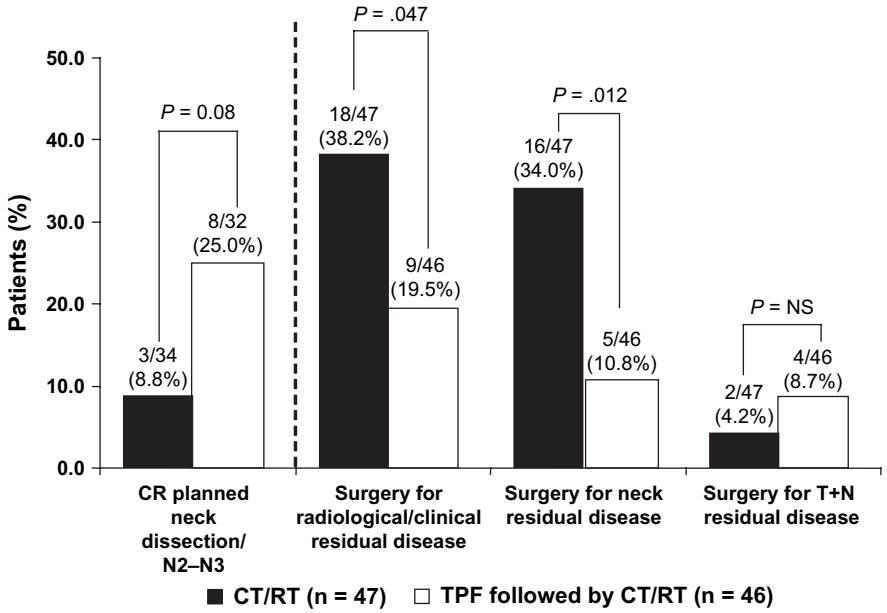

Figure 2. Proportion of patients undergoing surgery during the study. Patients with stage N2–N3 disease achieving a pathologically confirmed complete response (CR) at the primary site and a radiologic CR at the neck underwent prophylactic neck dissection. Surgery was considered for patients with recurrence at the primary site and/or residual disease after concomitant chemoradiotherapy (CT/RT) at one or both sites. Patients were treated with concomitant CT/RT alone or docetaxel, cisplatin plus 5-fluorouracil (TPF) induction therapy followed by concomitant CT/RT. NS, not significant.

superiority of induction PF plus docetaxel (TPF) before radiotherapy or chemoradiation in comparison to induction PF in response rate, TTP, and OS [10, 11]. However, a limitation of these studies was the absence of a standard control arm (CT/RT only), and consequently, no definitive conclusion is possible.

In our study, induction TPF followed by CT/RT more than doubled the CR rate 6–8 weeks after the end of the treatment compared with CT/RT alone. Notably, induction TPF was feasible and well tolerated and did not compromise the delivery of subsequent CT/RT.

Responses were radiologically evaluated 6–8 weeks after the end of treatment, consistently with the usual timing in clinical practice. However, no data on the best method and optimal timing for evaluating responses in SCCHN have been published to date. Randomized trials have used various methods (radiologic, endoscopic, and pathologic), limiting comparisons among different studies. Moreover, radiologic assessment (CT, MRI) of SCCHN is particularly difficult because of the anatomic characteristics of the region and the post-treatment changes that make image interpretation difficult. However, the effect of radiotherapy lasts long after the end of treatment, and late CRs due to subclinical damage of tumor cells have been frequently observed. Radiologic responses in our study were centrally reviewed by an internal committee in a blinded fashion to minimize possible bias. Some patients with a radiologic PR or stable disease at the first evaluation (6–8 weeks after treatment) became either a CR or PR when evaluated 8 months after the end of CT/RT, despite no additional treatment.

The present study indicates that induction chemotherapy may improve short-term locoregional control. Given the significantly lower number of surgical interventions for residual disease in induction arm, our study also indicates that induction TPF could reduce the need for surgery in patients with radiological/clinical residual disease following CT/RT. Patients with persistent disease following radical radiotherapy or CT/RT have a poor prognosis; however, except in laryngeal cancer, the benefit of palliative surgery is currently unclear. Thus, the potential ability of induction TPF to reduce the need for surgical palliation could be clinically meaningful.

It is well recognized that PF induction improves OS over radiotherapy alone mainly due to a reduction in distant metastases. Induction TPF seems to provide additional improvement in OS related to an increase in short-term locoregional control, as observed in the present study and in the Posner TPF trial (TAX 324) [11].

We consider two cycles of PF concurrent with standard fractionation radiotherapy an acceptable standard treatment regimen. Regarding radiation regimen, the meta-analysis of radiotherapy in carcinomas of the head and neck [21] showed a limited survival benefit for altered fractionated radiotherapy compared with standard fractions; after, a more detailed analysis, this advantage was confirmed only for hyperfractionated treatments, which are infrequently applied in clinical practice for practical reasons. However, data on local control and toxic effects favor altered fractionated radiotherapy, depending on the technique used. From the MACH-HN results, the best concomitant chemotherapy regimens are cisplatin alone or PF. The survival advantages are similar (11% and 10%, respectively) and, in our opinion, both options are acceptable chemotherapy regimens to combine with radiation. We previously conducted a phase I–II study to evaluate the feasibility of induction TPF followed by PF concomitant with radiotherapy [22] but had to reduce the number of planned chemotherapy cycles during CT/RT from

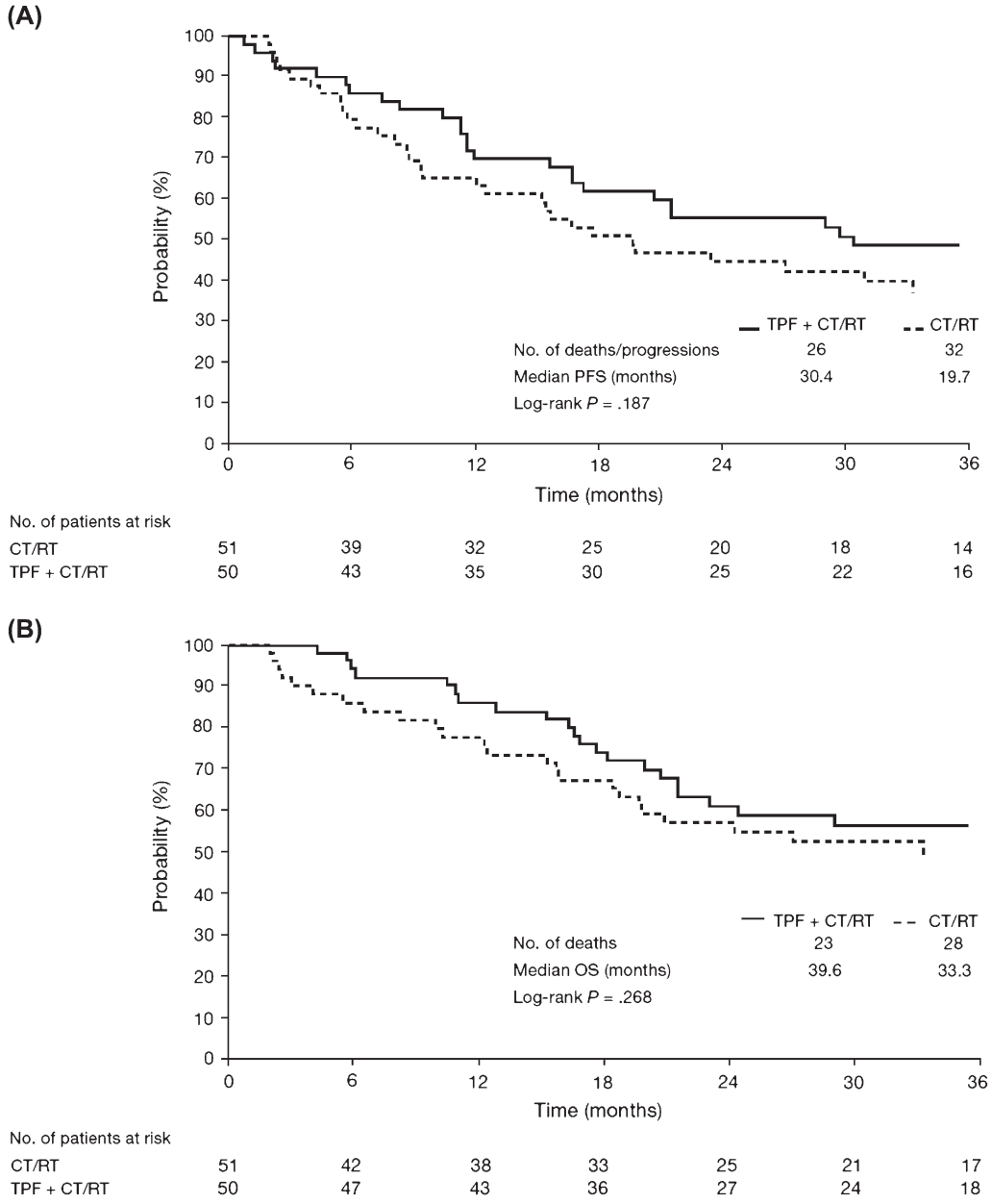

Figure 3. Kaplan–Meier plots of (A) progression-free survival (PFS) and (B) overall survival (OS) for all patients treated with concomitant chemoradiotherapy (CT/RT) versus docetaxel, cisplatin plus 5-fluorouracil (TPF) induction therapy followed by CT/RT.

three to two because toxicity interrupted planned radiotherapy. Whether three cycles of concomitant chemotherapy are superior to two cycles is an open question, and this issue has not been tested in phase III trials. At present, several institutions have adopted two cycles of cisplatin alone as standard concomitant chemotherapy for their phase III studies on the basis of published data on poor compliance with three chemotherapy cycles concomitant to radiation in either advanced or adjuvant settings [23]. We believe this is sufficient evidence to consider as appropriate the comparator arm of our study.

At the time our study was planned, results from a phase III trial comparing radiotherapy plus cetuximab versus radiotherapy alone in locally advanced SCCHN were not available. We now know that radiotherapy plus cetuximab provided superior OS and locoregional control compared with radiotherapy alone, without worsening radiotherapy-induced toxicity [24]. Radiotherapy plus cetuximab is now considered an alternative to CT/RT, although a direct comparison has not yet been carried out and the improved tolerability over CT/RT is only speculation. A proposed randomized, four-arm, factorial phase III trial will include a second randomization option, allowing a direct comparison of OS with induction chemotherapy versus no induction and of the infield toxicity of CT/RT versus radiotherapy plus cetuximab.

funding

Sanofi-Aventis, Italy

Table 3. Incidence of hematologic and non-hematologic grade 3–4 adverse events during CT/RT

NCIC CTG grade	CT/RT (arm A) ($N = 49$), n (%)			TPF + CT/RT (arm B) ($N = 43$), n (%)	
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4
Anemia	0	0	0	2 (4.5)	0
Neutropenia	2 (4.1)	2 (4.1)	0	2 (4.5)	0
Febrile neutropenia	0	0	0	0	0
Leukopenia	4 (8.2)	2 (4.1)	0	3 (6.9)	0
Thrombocytopenia	2 (4.1)	0	0	2 (4.5)	0
Mucositis/stomatitis	17 (34.7)	1 (2.0)	0	10 (23.2)	2 (4.5)
Dysphagia	7 (14.3)	3 (6.1)	0	6 (13.9)	3 (6.8)
Skin	5 (10.2)	1 (2.0)	0	8 (18.6)	0
Pain	4 (8.2)	1 (2.0)	0	3 (6.9)	1 (2.3)
Weight loss	1 (2.0)	0	0	2 (4.5)	0
Nausea/vomiting	0	0	0	0	0
Asthenia	3 (6.1)	1 (2.0)	0	1 (2.3)	0
Infection	0	0	1 (2.0)	0	0

CT/RT, concomitant chemoradiotherapy; NCIC CTG, National Cancer Institute of Canada—Clinical Trials Group; TPF, docetaxel, cisplatin plus 5-fluorouracil.

Table 4. Compliance with CT/RT

Compliance	CT/RT (arm A) ($N = 49$)	TPF + CT/RT (arm B) ($N = 43$)
Median dose RT, Gy (range)	70 (60–70)	70 (8–70)
Median duration of CT/RT, weeks (range)	7.7 (4–8)	7.6 (1–11)
Patients with radiotherapy interruption duration ≥3 days, n	16	17
Median duration of single radiotherapy interruption, days (range)	5 (3–8)	5 (3–10)
Concomitant two cycles of PF, n (%)	45 (91.8)	40 (93.0)

CT/RT, concomitant chemoradiotherapy; TPF, docetaxel, cisplatin plus 5-fluorouracil; RT, radiotherapy; PF, cisplatin plus 5-fluorouracil.

acknowledgements

We thank Ana Martinez-Bouteleux (Medical Director Sanofi-Aventis Global Oncology Franchise) for careful critical readings of the manuscript and many helpful suggestions. We also thank Laura McMahon (Clinica Research Cooordionator, Venice), Barbara Villa, Pietro Sganga, and Anna Torricelli (Sanofi-Aventis, Italy), and Chiara Sguotti for her backing and encouragement. An abstract and oral presentation including data from this study were presented at the 44th Annual Meeting of the American Society of Clinical Oncology, 2008.

disclosures

The following authors indicated a financial or other interest that is relevant to the subject matter under consideration in this article: AP reports a consultant or advisory role and receiving honoraria and research funding from Sanofi-Aventis, Merck Serono, Bristol Myers Squibb, and Lilly. MGG reports advisory role, honoraria, and research funding from Sanofi-Aventis, Merck, and Serono. DD is Scientific Oncology Manager for Sanofi-Aventis, Italy. Author contributions—Conception and design: A. Paccagnella, P. L. Zorat, G. Turcato, and M. G. Ghi. Collection and assembly of data: Quintiles Spa, A. Tinazzi (Chiquadrato Sendo Foundation), A. Paccagnella, M. G. Ghi, and D. Dondi. Data analysis and interpretation: A. Tinazzi and V. Torri (Chiquadrato Sendo Foundation), A. Paccagnella, M. G. Ghi, A. Buffoli, and L. Loreggian. Manuscript writing: AP and MGG. Final approval of manuscript: all authors.

references

1. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74–108.
2. Munrow AJ. A systematic review of chemotherapy trials in head and neck cancer. Eur J Cancer 1999; 35 (Suppl 4/9): S602a.
3. Bernier J, Domenge C, Eschwege F et al. Chemo-radiotherapy, as compared to radiotherapy alone, significantly increases disease-free and overall survival in head and neck cancer patients after surgery: results of EORTC phase III trial 22931. N Engl J Med 2004; 350: 1937–1944.
4. Cooper SJ, Pajak TF, Forastiere AA et al. Patterns of failure for resected advanced head and neck cancer treated by concurrent chemotherapy and radiation therapy: an analysis of RTOG 9501/intergroup phase III trial. N Engl J Med 2004; 350: 1945–1952.
5. Pignon JP, Bouhris J, Domenge C et al. 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: 949–955.
6. Wolf GT, Hong WK, Fisher SG et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991; 324: 1685–1690.
7. Forastiere AA, Goepfert H, Maor M et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003; 349: 2091–2098.
8. Lefebvre JL, Chevalier D, Luboinski B et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. J Natl Cancer Inst 1996; 88: 890–899.
9. Hitt R, López-Pousa A, Martínez-Trufero J et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin fluorouracil induction

chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005; 23: 8636–8645.
10. Vermorken JB, Remenar E, Van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357: 1695–1704.
11. Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357: 1705–1715.
12. Sobin LH, Wittekind C. UICC TNM Classification of Malignant Tumours, 5th edition. New York, NY: Wiley-Liss 1997.
13. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–216.
14. Brundage MD, Pater JL, Zee B. Assessing the reliability of two toxicity scales: implications for interpreting toxicity data. J Natl Cancer Inst 1993; 85: 1138–1148.
15. RTOG/EORTC Late Radiation Morbidity Scoring Schema. http://www.rtog.org/members/toxicity/late.html (20 June 2008, date last accessed).
16. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep 1985; 69: 1375–1381.
17. Bourhis J, Le Maître A, Baujat B et al. Individual patients' data meta-analyses in head and neck cancer. Curr Opin Oncol 2007; 19: 188–194.
18. Paccagnella A, Orlando A, Marchiori C et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancer: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. J Natl Cancer Inst 1994; 86: 265–272.
19. Zorat PL, Paccagnella A, Cavaniglia G et al. Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10-year follow-up. J Natl Cancer Inst 2004; 96: 1714–1717.
20. Domenge C, Hill C, Lefebvre JL et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC). Br J Cancer 2000; 83: 1594–1598.
21. Bourhis J, Overgaard J, Audry H et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006; 368(9538): 843–854.
22. Ghi MG, Paccagnella A, D'Amanzo P et al. Neoadjuvant docetaxel, cisplatin, 5-fluorouracil before concurrent chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck versus concomitant chemoradiotherapy: a phase II feasibility study. Int J Radiat Oncol Biol Phys 2004; 59: 481–487.
23. Huguenin P, Beer KT, Allal A et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancer treated with hyperfractionated radiotherapy. J Clin Oncol 2004; 22: 4665–4673.
24. Bonner J, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354: 567–578.

appendix

The following investigators and centers also participated in the trial: R. La Bianca, A. Mazzoni, A. Personemi (Bergamo); M. Righi, G. Frezza (Bologna, Bellaria); U. Caliceti, L. Crinò, I. Ammendolia (Bologna, Malpighi); F. Gaion, F. Polidoro (Camposampiero); M. Amichetti, V. Mascia, G. Tore (Cagliari); F. Bagatella, P. Manente (Castelfranco Veneto); D. Ferraro, T. Franceschi (Legnago); E. Aitini, A. Di Marco, N. Taurozzi (Mantova); G. Bonciarelli, F. Lunghi (Monselice); F. Parmigiani (Monza); Maria Luisa Friso, A. Scola, G. Sotti, A. Staffieri (Padova); V. Migliorini, G. Pavanato (Rovigo); C. Grandi, F. Valduga (Trento); S. Lamon, C. Marchiori (Treviso), F. Boetner, G. B. Pizzi (Mestre, Venezia); F. Bordin, P. D'Amanzo, F. Maccarrone, C. Mastromauro, G. Turcato (Venezia); A. Beorchia, M. Russolo, G. Tuveri (Trieste).