Chemotherapy can be administered in patients with locoregionally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN) either concurrently with irradiation or as induction chemotherapy prior to local treatment or as palliative therapy in patients with recurrent and/or metastatic disease. Cisplatin-based chemoradiation is still the standard for LA–SCCHN. TPF has emerged as the new standard regimen when induction chemotherapy is indicated. Areas of active investigation in LA–SCCHN are the sequential administration of induction chemotherapy followed by chemoradiation and the integration of targeted therapies. None of the combination chemotherapy regimens demonstrated an overall survival benefit when compared to single agent methotrexate, cisplatin or 5-fluorouracil in recurrent/metastatic disease. Combination chemotherapy in this setting is preferably used in younger patients with a good performance status and with symptomatic disease who require prompt symptom relief. However, a survival benefit was observed when cetuximab was combined with platinum-5-fluorouracil.

**Introduction**

The role of chemotherapy is slowly moving towards a more prominent position within the different treatment paradigms in patients with squamous cell carcinoma of the head and neck (SCCHN). This is particularly true for the locoregionally advanced (LA) disease condition in which chemotherapy may be given either concurrently with irradiation (as definitive treatment or postoperatively) or before (induction) or after (adjuvant) locoregional treatment as a single modality. However, also at last in the recurrent/metastatic setting results are changing with the introduction and integration of molecular targeting therapies.1,2

**Locoregionally advanced squamous cell carcinoma of the head and neck**

Two-thirds of the SCCHN are in a LA stage at time of diagnosis. Treatment paradigms in that setting include various forms of curative combined modality therapies, including concurrent chemoradiation (or biochemoradiation), induction chemotherapy followed by irradiation and sequential therapy (induction chemotherapy followed by concurrent chemoradiation). The role of bio(chemo)radiation will be discussed in the separate chapter on targeted therapies in this issue.

**Concurrent chemoradiation**

Concurrent chemoradiation was widely adopted as standard of care for LA–SCCHN after the publication of a large meta-analysis based on individual data of 10,741 patients in 63 randomized trials.3 The meta-analysis was recently updated and extended to 16,640 patients treated in 87 trials.4 Concurrent chemoradiation conferred an absolute survival benefit of 8% at 2 and 5 years.3,4 Chemotherapy even improves survival when added to hyperfractionated or accelerated radiotherapy which itself is superior to conventional radiation alone.5,6 Multiple randomized phase III trials demonstrated a survival benefit for chemoradiation over radiation alone, administered either as definitive treatment7–18 or in the adjuvant setting, after surgery, for high risk patients.19,20 The best studied and most widely used regimen, which can be considered the standard comparator for randomized trials, is cisplatin 100 mg/m² on days 1, 22 and 43. A survival benefit in single randomized trials has also been suggested with daily low dose cisplatin,9 weekly intermediate dose cisplatin,10 cisplatin 20 mg/m² day 1–5 and day 29–3311 and 5-fluorouracil combined with either cisplatin,12–14 carboplatin15,16 or mitomycin C.17 Promising results in non-randomized studies were reported with multiple single agents including weekly low dose gemcitabine,21 weekly docetaxel,22 weekly paclitaxel,23 carboplatin18,24,25 and with combinations as TFHX (paclitaxel, 5-fluorouracil and hydroxyurea).26,27
Induction chemotherapy

Rationale

Induction chemotherapy has some appealing theoretical advantages such as optimal drug delivery to the tumor through disrupted vasculature, early eradication of micrometastases and improved tolerance of cytotoxic drugs. Moreover, induction chemotherapy offers the opportunity of assessing tumor response and thereby selecting the patients for organ preservation.

Organ preservation

Organ preservation was pioneered by the Veterans Affairs Laryngeal Cancer Study Group which randomized 332 patients between laryngectomy and induction chemotherapy followed by definitive radiation. After a follow-up of 33 months the estimated 2 year survival was 68% for both treatment groups. The larynx was preserved in 64% of the patients in the induction chemotherapy arm. There were significantly more distant metastases in the surgery group and more locoregional recurrences in the chemotherapy group. After the publication of the results of the trial, induction chemotherapy followed by radiation was widely adopted as an alternative for laryngectomy for patients with LA. The larynx was preserved in 64% of the patients in the induction chemotherapy arm. There were significantly more distant metastases in the chemotherapy arm preserved their larynx. However, the 2 year disease progression or a relapse. Only 14% of them had distant metastases. Fifty-three percent of the patients in arm A and 16% in arm B were treated off protocol. Median time to treatment failure was 12 months in arm A and 20 months in arm B (p = 0.003). Patients in arm B had a trend to longer overall survival although the difference was not significant. However, the difference in median overall survival (26 vs. 36 months) was statistically significant for patients with unresectable disease. After a median follow-up of 23 months, 175 patients had disease progression or a relapse. Only 14% of them had distant metastases. Fifty-three percent of the patients in arm A and 16% in arm B experienced grade 2, 3 or 4 mucositis during induction chemotherapy (p < 0.001). Vermorken et al. randomized 358 patients with locoregionally advanced unresectable squamous cell carcinoma of the head and neck between four cycles of PF or TPF (docetaxel 75 mg/m2 and cisplatin 75 mg/m2 on day 1 followed by 5-fluorouracil 750 mg/m2/day on day 1–5 administered as a continuous infusion on day 2–6) (PPF) (arm B) as induction regimen. Thirty-five percent of the patients had resectable disease. The primary objective was to compare the complete response rate which was 14% in arm A and 33% in arm B (p < 0.001). Patients with a complete response or a partial response of at least 80% at the primary tumor site were treated with chemoradiation (conventional radiation, 70 Gy and cisplatin 100 mg/m2 on days 1, 22 and 43). Patients with a less than 80% response or stable disease in the lymph nodes were referred for radical neck dissection. Patients with no response in the primary tumor or progressive disease in the lymph nodes or the primary tumor were taken off study and treated according to the institutions guidelines. Ninety five of the 193 patients in arm A and 56 of the 189 patients in arm B were treated off protocol. Median time to treatment failure was 12 months in arm A and 20 months in arm B (p = 0.003). Patients in arm B had a trend to longer overall survival although the difference was not significant. However, the difference in median overall survival (26 vs. 36 months) was statistically significant for patients with unresectable disease. After a median follow-up of 23 months, 175 patients had disease progression or a relapse. Only 14% of them had distant metastases. Fifty-three percent of the patients in arm A and 16% in arm B experienced grade 2, 3 or 4 mucositis during induction chemotherapy (p < 0.001). Vermorken et al. randomized 358 patients with locoregionally advanced unresectable squamous cell carcinoma of the head and neck between four cycles of PF or TPF (docetaxel 75 mg/m2 and cisplatin 75 mg/m2 on day 1 followed by 5-fluorouracil 750 mg/m2/day on day 1–5 administered as a continuous infusion). After induction chemotherapy, all patients with stable or responsive disease were irradiated (conventionally fractionated, hyperfractionated or accelerated). After a median follow-up of 32 months, the progression free survival (primary endpoint) was found significantly longer in the TPF arm (11 vs. 8.2 months, p = 0.007). After a median follow-up of 51 months, median overall survival in the TPF arm was 18.6 months vs. 14.2 months in the PF arm (p = 0.0052). Estimated 3 year overall survival was 36.5% for TPF and 23.8% for PF. Grade 3/4 neutropenia was more...
frequent with TPF (76.9% vs. 52.5%), while thrombocytopenia was more frequent with PF (17.9% vs. 5.2%) and there were less toxic deaths observed in the TPF arm (2.3% vs. 5.5%). Moreover the quality of life was better preserved in the TPF arm. Posner et al. randomized 539 patients to TPF (docetaxel 75 mg/m² and cisplatin 100 mg/m² on day 1 followed by 5 FU 1000 mg/m²/day for 4 days) or PF. Eligible were patients with resectable disease with low cure rate, patients with unresectable disease and patients who were candidates for organ preservation. After 3 cycles patients received chemoradiation with weekly carboplatin. After a median follow-up of 42 months the median overall survival (primary end-point) was 70.6 months in the TPF arm vs. 30.1 months in the PF arm (p = 0.0058). Three-year overall survival and progression free survival (PFS) were 62% and 48%, respectively. Grade 3/4 neutropenia was more common in the TPF arm than in the PF arm (84% vs. 56%). Calais et al. presented data on a larynx preservation trial with TPF in patients with operable stages III or IV carcinoma of the larynx or hypopharynx who required total (pharyngo)laryngectomy. Two hundred and twenty patients were randomized between TPF and PF. After 3 cycles patients with a less than 50% tumor reduction and/or persistent larynx fixation underwent total laryngectomy followed by radiotherapy while the responders received radiation alone. The overall response rate was 82.8% with TPF and 60.8% with PF. Larynx preservation after induction was offered to 80% of the patients in the TPF arm and to 57.6% in the PF arm. After a median follow-up of 45 months the actuarial 3 year larynx preservation rate was 74% with TPF and 51% with PF (p = 0.036). Overall survival was not different between the two arms of the study. Other alternatives for PF were less successful. Rivera et al. randomized 206 patients with LA–SCCHN to 4 cycles of PF or UFTVP (UFT 200 mg/m²/day on day 1–21, cisplatin 100 mg/m² on day 1 and vinorelbine 25 mg/m² on day 1 and 8 of each 21 day cycle), followed by (chemo)radiation or surgery. This phase II study failed to meet its primary endpoint which was improved complete response rate; however, UFTVP was associated with an improved overall survival (hazard ratio: 0.67; p: 0.03). Fonseca et al. randomized 83 patients with LA–SCCHN between docetaxel 85 m/m² on day 1 with cisplatin 40 mg/m² on day 1 and 2 (arm A), every three weeks, or PF (arm B). The overall response rate and complete response rate were 70% and 26%, respectively, in arm A and 69% and 16%, respectively, in arm B. The most frequent grade 3/4 toxicity in arm A was neutropenia (34.1%) and diarrhoea (9.8%) vs. neutropenia (19.5%) and mucositis (29.3%) in arm B. Both schedules present a similar efficacy, with different but acceptable toxicity patterns.

Sequential treatment

Multiple phase II trials as well as the randomized trials by Posner et al. and by Hitt et al. clearly demonstrated the feasibility of TPF or PPF induction chemotherapy followed by concurrent chemoradiation. However, all the above-mentioned randomized trials compared two different induction regimens and were not designed to compare induction therapy or sequential treatment, i.e., induction chemotherapy followed by chemoradiation, to chemoradiation alone. At least five large randomized phase III trials comparing TPF induction chemotherapy followed by chemoradiation to chemoradiation alone are currently planned or underway. Preliminary data of a trial conducted by the Spanish Head and Neck Cancer Cooperative Group were presented at ASCO 2006. Patients were randomized to receive either TPF or PF induction chemotherapy followed by chemoradiation or chemoradiation alone. Median time to treatment failure was 16 months in the TPF arm, 12 months in the PF arm and 8 months in the chemoradiation alone arm. However suggestive, further maturation of the data is warranted before making definitive conclusions. A particular question is whether the relapses are prevented or merely postponed by a time period equivalent to the induction chemotherapy period. Anyway, the pattern of relapse differed clearly between the three arms: locoregional relapses were more common in the induction chemotherapy arms while distant metastasis were far more frequent in the chemoradiation alone arm. Paccagnella et al. presented the phase II portion of an Italian multicenter trial. Patients were randomized to receive 3 cycles of TPF followed by conventional radiotherapy concurrently with 2 cycles of PF or the same chemoradiation alone. The complete response rate was 46.8% in the induction arm and 19% in the CRT arm. This trial has subsequently been taken into phase III.

Recurrent disease

While the vast majority of the patients presenting with stage I and II SCCHN will remain disease free after surgery and/or radiotherapy, the majority of patients presenting in a more advanced disease stage will eventually relapse either locoregionally and/or at distant sites. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation. However, most patients with recurrent or metastatic disease only qualify for palliative treatment. Treatment options in these patients include supportive care only, single agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents. Treatment choice should be based on factors such as performance status, comorbidity, prior treatment, symptoms and patient preference.

Single agent cytotoxic therapies

The four most extensively studied single cytotoxic agents are bleomycin, methotrexate, 5-fluorouracil and cisplatin. Response rates with these agents in patients with recurrent and/or metastatic SCCHN are generally in the 15 to 30% range, while response duration is generally between three and five months. Similar response rates, mostly in phase II studies, were observed with newer agents such as paclitaxel, docetaxel, vinorelbine, irinotecan, pemetrexed and gemcitabine. Grose et al. randomized 100 patients to be treated either with methotrexate or cisplatin. Response rates were 16% and 8%, median durations of response were 18 and 8 weeks and median durations of survival were 20 weeks and 18 weeks, with methotrexate and cisplatin, respectively. A similar but smaller study was conducted by Hong et al. They found neither a difference in objective response rate nor in median overall survival. However, mucositis occurred more frequently in the methotrexate group (38% vs. 0%; p = 0.001), while vomiting occurred more frequently in the cisplatin group (87% vs. 10%; p < 0.0001). These two randomized studies demonstrated that in the treatment of recurrent SCCHN, methotrexate and cisplatin are equally effective, although methotrexate appears to be better tolerated. The taxanes are among the most active cytotoxic drugs in SCCHN. Vermorken et al. compared paclitaxel 175 mg/m² administered either as a 3 h or a 24 h infusion, with standard-dose methotrexate (40–60 mg/m² weekly) in a randomized phase II study. The 24 h infusion regimen was considered too toxic due to a high incidence of febrile neutropenia. None of the regimens was superior with respect to response or survival. Weekly schedules of taxanes induce interesting response rates, even in pretreated patients and may have a better therapeutic index than three-weekly schedules. Guardiola et al. randomized 57 patients between weekly docetaxel 40 mg/m² or weekly methotrexate 40 mg/m². The overall response rate in this phase II trial was significantly higher with docetaxel (27% vs. 15%). However, there was no indication that overall survival or time to progression was any different between the two treatment arms. It is currently unclear if
any of the cytotoxic agents prolongs survival when compared with supportive care alone as an adequately powered randomized controlled trial has never been performed.

Combination chemotherapy

Standard combinations

Several of the more traditionally used combination chemotherapy regimens have demonstrated higher response rates when compared to either cisplatin or methotrexate alone albeit at the cost of a greater toxicity. Moreover, none of these trials could demonstrate a survival advantage with the combination regimens. The combination of cisplatin, bleomycin and methotrexate was compared to weekly methotrexate in a randomized prospective trial in 163 patients. The combination produced a 48% response rate compared to 35% for methotrexate alone (p = 0.04). However, median survival was the same (5.6 months) in both arms. Chauveau et al. randomized 209 patients to receive either cisplatin alone or in combination with vincristine, bleomycin and methotrexate. The response rate was higher with the combination (30% vs. 15%; p = 0.01); however, the tolerance was significantly better with cisplatin alone. There was neither a difference in median duration of response nor in overall survival between the two arms of the study. Clavel et al. randomized 185 patients between CABO, which consisted of cisplatin, methotrexate, bleomycin and vincristine, and ABO (CABO without cisplatin). Although the overall response rate was higher with CABO (50% vs. 28%; p = 0.003), this did not lead to a better survival. The PF combination gradually emerged as the most commonly used combination chemotherapy regimen in SCCHN. In a next phase III study Clavel et al. compared PF with CABO and with cisplatin alone in 302 patients with metastatic or recurrent SCCHN. The overall response rate was 31% with PF, 34% with CABO and 15% with cisplatin alone. The two combination regimens were significantly better than cisplatin alone (p < 0.001 and 0.003, respectively). In addition, the complete response rate with CABO (9.5%) was higher than with cisplatin alone (2.5%) (p = 0.02), or with PF (1.7%) (p = 0.01). However, again, these higher response rates did not translate into an improved median survival, which was 7.3 months in all three arms. The median time to progression (TTP) among the assessable patients was 19 weeks in the CABO arm, 17 weeks in the PF arm and 12 weeks in the cisplatin arm (log rank p = 0.2). Both combination regimens were associated with more toxicity. The Liverpool Head and Neck Oncology Group randomized 200 patients between to receive either cisplatin alone or methotrexate alone or cisplatin plus methotrexate or PF. There was no significant difference in the response rates. They reported a survival benefit for the cisplatin alone arm compared with metotrexate alone. Nausea/vomiting and anemia were significantly more common in the cisplatin arms than in the methotrexate arm. Forastiere et al. randomized 277 patients to PF, carboplatin/5-fluorouracil (CF) or standard dosed methotrexate. Hematologic and nonhematologic toxicities were significantly worse with PF than with methotrexate (p = 0.001). Toxicity with CF was intermediate between the two other regimens. The response rates were 32% for PF, 21% for CF, and 10% for methotrexate, respectively. The comparison of PF to methotrexate was statistically significant (p < 0.001), and the comparison of CF to methotrexate was of borderline statistical significance (p = 0.05). Median response durations and median survival times were similar for all three treatment groups. The CF combination also induced fewer responses than the PF regimen in a randomized phase III trial in the neoadjuvant setting. Moreover, there was no difference in response rate in a randomized comparison of carboplatin plus methotrexate vs. single-agent methotrexate. Taken together, these data clearly suggest that carboplatin is less active than cisplatin in the treatment of SCCHN. Jacobs et al. compared the PF regimen with either cisplatin alone or 5-fluorouracil alone in a randomized phase III trial which included 249 patients. The overall response rate to PF (32%) was superior to that of cisplatin (17%) or 5-fluorouracil (13%) (p = 0.035). However, there was neither a difference in median time to progression nor survival among the three groups.

Novel combinations

Several investigators substituted 5-fluorouracil by oral fluoropyrimidines. Rurousso et al. combined cisplatin with capecitabine and observed an overall response rate of 48%. Median TTP was 3.5 months and median overall survival time was 12.4 months. Grade 3/4 neutropenia, anemia and thrombocytopenia were observed in 17%, 13% and 1% of cycles, respectively. Grade 4 anemia was observed in 8% of patients. Grade 3/4 asthenia, nausea, vomiting, stomatitis, diarrhea and hand foot syndrome were observed in 12%, 12%, 8%, 4% and 4% of patients, respectively. Gil-Negrete et al. observed an overall response rate of 46% and 7.7% complete responses with a combination of docetaxel 75 mg/m2 on day 1 and capecitabine 950 mg/m2/12 h on days 2–14. However, the regimen was too toxic with 7.7% toxic deaths. Bentzen and Hansen treated 50 chemonaive patients with paclitaxel 175 mg/m2 i.v. on day 1 and capecitabine 825 mg/m2 bid for 2 weeks. Cycles were repeated every three weeks. Overall response rate was 42% with 4% complete responses. Median TTP was 5.2 months and median overall survival was 8.2 months. The regimen was well tolerated with grade 3/4 toxicities including hand-and-foot syndrome (12%) and neutropenia (18%). S-1 is an oral fluoropyrimidine with promising single agent activity in SCCHN with reported response rates ranging between 28% and 57% when it was administered as a single agent. Maruoka et al. combined the cisplatin analog nedaplatin 80–100 mg/m2 with either 5-fluorouracil 600 mg/m2/day on days 1–5 or S 1 60–80 mg/m2 bid on days 1–14 in 32 patients with previously untreated oral SCC. Cycles were repeated every 4 weeks and the investigators and observed an overall response rate of 72% and 64%, respectively. Both regimens were well tolerated.

The taxanes have been combined with a platinum compound by several investigators. The carboplatin/docetaxel combination was evaluated in a phase II study conducted by the Southwest Oncology Group. Sixty-eight patients were treated with docetaxel 65 mg/m2 and carboplatin AUC 6 every 21 days. The overall response rate was 25%. Sixty-one percent of the patients experienced grade 3/4 neutropenia. The median PFS was 3.8 months and the median overall survival 7.4 months. The paclitaxel plus cisplatin combination was directly compared to the PF regimen in the Intergroup trial E1395 conducted by the Eastern Cooperative Oncology Group. Patients received either paclitaxel 175 mg/m2 (over 3 h) and cisplatin 75 mg/m2, both on day 1 (OP) or OP. The objective response rate was 27% with PP and 26% with PF. The overall grade 3/4 toxicity rate was similar between the two groups. However, grade 3/4 mucositis (31%) was only observed in the PF arm, while the occurrence of neurotoxicity was similar in the two groups. Median overall survival was 8.7 months in the PF group and 8.1 month in the PP group. Considering the more favourable toxicity profile, PP may be a valuable alternative to PF.

The Hellenic Cooperative Oncology Group randomized 166 patients with SCCHN between two taxane-based experimental regimens consisting of paclitaxel 175 mg/m2 on day 1 and gemcitabine 1000 mg/m2 on days 1 and 8 every three weeks or paclitaxel 175 mg/m2 on day 1, and pegylated liposomal doxorubicin 40 mg/m2 on day 1 every four weeks. There was no significant difference in response rate (20% vs. 25%, p = 0.21), median TTP (4.4 months vs. 6.0 months, p = 0.08) or median overall survival (8.6 months vs. 11.05 months, p = 0.25). Overall, there was no significant difference in severe toxicity between the two treatment arms.
Randomized studies comparing each of the two regimens with standard chemotherapy are needed before they can be recommended outside a clinical trial. The combination of oxaliplatin and 5-fluorouracil with folinic acid was tested in a phase II trial at Charité Universitätsmedizin Berlin. The overall response rate was 60.6% with 21.2% complete responses. The median TTP was 8.1 months and the median overall survival was 10.8 months. The incidence of hematologic toxicity was low but mild paresthesias occurred in all patients who received more than three cycles. Labourey et al. treated 40 patients with a combination of docetaxel 75 mg/m² (day 8) and gemcitabine 1000 mg/m² (days 1 and 8) every three weeks for six cycles. The overall response rate was 20.0%. The median response duration was 6.5 months. Grade 3 or 4 neutropenia was observed in 18 patients (45.0%). Moreover, three treatment-related deaths due to infection were reported. Xydkakis et al. treated 21 patients who had relapsed after first-line platinum-containing treatment with methotrexate 30 mg/m² and gemcitabine 800 mg/m² on days 1, 8, and 15 in cycles of 28 days. The overall response rate was 14%. Mean TTP of all patients was eight months while mean overall survival was 14 months. As already mentioned, the superiority of TPF and PPF over PF administered as induction chemotherapy for patients with LA–SCCHN has recently been demonstrated in large randomized phase III trials. In the recurrent/metastatic disease setting these triplets have also shown promising results. With TPF, Janinis et al. observed an overall response rate of 44%, a median TTP of 7.5 months and a median overall survival of 11 months. Febrile neutropenia occurred in 15% of the patients. Benasso et al. treated 47 patients with PPF (paclitaxel 160 mg/m² on day 1 and cisplatin 25 mg/m²/day and 5-fluorouracil 250 mg/m²/day, both on days 1–3), every three weeks. The overall response rate was 31% with 13.3% complete responses. Median PFS and overall survival were 4.1 and 7.9 months, respectively. Forty-eight percent of the patients experienced grade 3/4 neutropenia. The TIP and TIC regimens were tested by Shin et al. The TIP regimen consisted of paclitaxel 175 mg/m² on day 1, ifosfamide 1000 mg/m² (by 2-h infusion) on days 1–3, mesna 600 mg/m² on days 1–3 and cisplatin 60 mg/m² on day 1, repeated on day 22. Ninety percent of the patients experienced grade 3 or 4 neutropenia and the rate of febrile neutropenia was unacceptable high (27%). The overall response rate was 58% with 17% complete responses. In the TIC regimen similar doses of paclitaxel and ifosfamide were used as in TIP, but cisplatin was replaced by carboplatin AUC 6. Also TIC was repeated every three weeks. TIC induced febrile neutropenia in 30% of the patients and one patient died of neutropenic sepsis. The overall response rate was 59% with 17% complete responses. The median duration of the responses was 3.7 months. Overall, it can be concluded that taxane containing triplets induce high response rates, also in the recurrent/metastatic disease setting. However, they are associated with substantial hematologic toxicity and a high complication rate. As these triplets have never been directly compared with PF in a randomized phase III study in this setting, they should not be recommended outside clinical trials. Moreover, as none of the combination chemotherapy regimens demonstrated an overall survival benefit when compared to single agent methotrexate, cisplatin or 5-fluorouracil, the use of combination chemotherapy preferably is used in younger patients with a good performance status and with symptomatic disease who require prompt symptom relief.

Combination of chemotherapy with targeted therapies

Targeted therapies are discussed in a separate chapter in this issue. The most promising data on targeted therapies in SCCHN have been observed with the anti-EGFR monoclonal antibodies. The combined use of chemotherapy and anti-EGFR antibodies is strongly supported by preclinical data and, recently, by randomized phase III studies in the recurrent/metastatic disease setting. In the EXTREME study, 442 patients were randomized to receive either chemotherapy alone (cisplatin 100 mg/m² or carboplatin AUC 5 on day 1 followed by 5-fluorouracil 1000 mg/m²/day for 4 days) or the same regimen combined with weekly cetuximab, a EGFR directed chimeric monoclonal antibody. Cycles were repeated every three weeks for a maximum of six cycles. Thereafter, in the combined arm, cetuximab was continued as a single agent until disease progression or unacceptable toxicity whatever came first. No crossover was permitted in this study. Excluded were patients who had received prior chemotherapy except when this had been part of their primary treatment provided this chemotherapy was ended at least six months before inclusion in the study. The primary endpoint was overall survival. The addition of cetuximab increased the median overall survival by 2.7 months from 7.4 to 10.1 months (hazard ratio 0.797, p = 0.036). With addition of cetuximab, the response rate increased from 19.5% to 35.6% (p < 0.0001) and the median PFS was prolonged from 2.3 months from 3.3 to 5.6 months (p < 0.0001). The addition of cetuximab did not modify the characteristic adverse event profile of platinum-based chemotherapy and did not have a negative impact on quality of life.

Conclusions

We conclude that cisplatin-based chemoradiation is still the standard approach for the treatment of LA–SCCHN. TPF has emerged as the new standard regimen when induction chemotherapy is appropriate. Areas of active investigation in LA–SCCHN are the sequential administration of induction chemotherapy followed by chemoradiation and the integration of targeted therapies. None of the combination chemotherapy regimens demonstrated an overall survival benefit when compared to single agent methotrexate, cisplatin or 5-fluorouracil in recurrent/metastatic disease. Combination chemotherapy in this setting is preferably used in younger patients with a good performance status and with symptomatic disease who require prompt symptom relief. However, a survival benefit was observed when cetuximab was combined with platinum-5-fluorouracil regimens. This is the first time in 25 years that superiority of a new regimen over standard platinum-based chemotherapy has been observed.

Conflict of interest statement

None declared.

References


