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Systematic review

Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials

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ABSTRACT

Background: Induction chemotherapy with docetaxel, cisplatin and 5 FU (TPF) before radiotherapy (RT) or radio-chemotherapy (RT-CHX) has been shown to improve overall survival (OS) compared to induction chemotherapy with cisplatin and 5 FU in locally advanced squamous cell carcinoma of the head and neck (HNSCC). Whether TPF induction before RT-CHX improves clinical outcome in comparison with RT-CHX alone is still a matter of debate. Recently, the results of 5 randomized trials addressing this question have become available.

Methods: In the 5 trials of interest, in total 1022 patients with locally advanced HNSCC were randomly assigned to receive either TPF induction CHX followed by concurrent RT-CHX or concurrent RT-CHX alone. Platin or taxane based CHX was used during RT. 51.3% of the patients had oropharyngeal, 7.3% hypoharyngeal, 18.7% laryngeal, 19.4% oral cavity and 3.5% had other HNSCC. Published hazard ratios and hazard ratios extracted from available survival curves for OS and progression free survival (PFS) were basis of the meta-analysis. Meta-analysis of the effect sizes on OS and PFS was performed using a random effects model based on parameter estimates of log hazard ratios in Cox models and their standard errors.

Results: Additional induction CHX with TPF before RT-CHX did neither result in a significant improvement of OS (Hazard Ratio: 1.010, 95% confidence limits (CL) 0.84–1.21, $p = 0.92$), nor in a statistically significant benefit of PFS (Hazard Ratio: 0.91, 95% CL 0.75–1.1, $p = 0.32$).

Conclusion: Additional induction CHX with TPF before RT-CHX does not improve OS and PFS in locally advanced HNSCC compared to definite RT-CHX.

Patients with advanced head and neck squamous cell cancer (HNSCC) have still a relative poor clinical outcome [1–9]. One standard treatment of resectable, stage III–IVb disease is surgery with or without adjuvant radiotherapy (RT) or adjuvant radio-chemotherapy (RT-CHX) [10]. The other opportunity is a primary radio-chemotherapy. More than 50% of patients with HNSCC will be diagnosed with locoregionally advanced and technically unresectable disease, or a resection will lead to a significant mutilation or a bad functional outcome as well as having a high risk of non in sano resection [11]. Randomized trials have shown that cisplatin containing chemotherapy (CHX) administered concurrently to RT improves OS in HNSCC-patients treated either by surgery and adjuvant RT-CHX or definite treatment with RT-CHX [12]. Conversely, adjuvant CHX after completion of adjuvant or definite RT does not improve clinical outcome [12]. Induction CHX with cisplatin and 5-FU before definite treatment with RT was associated with a small benefit in OS mainly as the consequence of a reduced distant failure rate [12]. Adding docetaxel to induction therapy with cisplatin and 5-FU (TPF) before RT or RT-CHX resulted in a significant improvement in OS in two large randomized phase III trials [2,11] and reduced significantly the incidence of distant

The preliminary results of this work were presented at the Annual ASCO meeting in the highlighted poster session 2014 in Chicago and the updated results at the Annual ESTRO meeting 2015 in Barcelona in the plenary session.

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metastases. A meta-analysis of individual patient's data of patients with HNSCC evaluating the question whether adding a taxane (paclitaxel or docetaxel) to induction PF indicated a substantial benefit in terms of OS, PFS, and locoregional tumor control was performed by Blanchard et al. [13]. Although these data indirectly suggest that induction therapy with TPF before definite RT-CHX could also improve clinical outcome compared to RT-CHX as sole treatment, this hypothesis needs confirmation by direct randomized comparisons. Recently, the results of a number of randomized trials comparing TPF induction before RT-CHX to RT-CHX have become available [14–18] and prompted us to perform a meta-analysis.

Patients, material and methods

A Pubmed search using the term "head and neck" and "radiotherapy" and "induction or neoadjuvant" and "randomized or randomised" was performed. Randomized phase II and III trials testing TPF induction CHX before RT-CHX versus RT-CHX in locally advanced head and neck squamous cell carcinoma of the head were of interest. In addition, a hand search using the references of recently published reviews, ASCO abstracts, and the knowledge of the authors was performed. Trials with other induction treatments than TPF or not using RT-CHX after induction TPF in the standard treatment arm were not eligible. In total 6 randomized trials including an update of one of the trials were identified [19,18,15,14,20,21]. The quality of the available information was evaluated according to the Cochrane guidelines [22]. Especially this includes that assigned to treatments needed to be done randomly, risk factor between treatment arm evenly distributed, exclusion of patients from the analysis adequate, and analysis performed on an intent to treat basis. Five trials met the criteria to be included, whereas one trial, published by Chen et al. [21] in Chinese language in a journal not listed in Pubmed, had to be excluded, since the provided information in the English abstract and the included tables and figures was found not sufficient to judge whether risk factors were well balanced and whether an intent to treat analysis was performed. Furthermore, a reliable estimate of the hazard ratios for OS and PFS with its confidence limits was not possible.

In the remaining 5 trials included in the meta-analysis, data on OS were available from 1022 patients and data on PFS on 862 patients with locally advanced HNSCC. All patients were randomly assigned to obtain either TPF induction CHX followed by concurrent RT-CHX or simultaneous RT-CHX alone.

Cohen et al. [19] randomized 285 patients with N2/N3 HNSCC either to docetaxel based concurrent RT-CHX or to induction CHX followed by the same RT-CHX. Induction CHX consisted of 2 cycles of docetaxel (75 mg/m^2 on day 1), 5-FU (750 mg/m^2/24 h on day 1–5) and cisplatin (75 mg/m^2 on day 1). For concurrent RT-CHX docetaxel (25 mg/m^2 one day), 5-FU (600 mg/m^2 for 6 days) and hydroxyurea (500 mg/m^2 per os 12 h for 6 days) were administered. RT was applied twice daily with 1.5 Gy to total doses of 74–75 Gy. Recorded risk factors were well balanced between treatment groups and according to the consort diagram exclusions from analysis were reasonable. An intent to treat analysis was performed. TPF induction resulted in a minimally statistically not significant improvement of OS and PFS. The rate of distant failure as first event was significantly lower after induction therapy.

Due to slow accrual the initial statistics of the trial was amended to include 280 patients instead of 400 patients. In addition, the event rate was lower than expected resulting in low power to detect a possible benefit of TPF induction.

Takácsi-Nagy et al. [18] randomly allocated 66 patients with locally advanced tumors in a phase II trial to receive either 2 cycles of TPF or not prior to RT-CHX consisting of planned 70 Gy in conventional fractionation and 3 cycles of 100 mg/m^2 cisplatin. Three patients were excluded, because they did not show up for any treatment. Risk factors were well balanced between groups. Analysis was performed as intent to treat. TPF induction therapy was associated with a statistically not significant trend toward poorer OS and PFS. The average dose of RT was considerably lower after induction CHX and 3 patients in the TPF arm died from febril neutrocytopenia. The latter resulted in a premature closure of the trial of 66 patients instead of the 99 initially planned.

Hitt et al. compared induction TPF followed by RT-CHX versus RT-CHX in HNSCC [15]. 439 patients were randomly assigned to induction CHX (classical schedule containing three cycles), with either docetaxel (Taxotere), cisplatin and 5-fluorouracil (TPF arm) or cisplatin and 5-fluorouracil (PF arm), followed by RT-CHX [70 Gy in 7 weeks of RT with cisplatin 100 mg/m^2 on day 1, 22 and 43]; or 7 weeks of RT-CHX alone. The primary endpoints were PFS and time-to-treatment failure (TTF). Risk factors were well balanced between the 3 arms of the study. The consort diagram indicates that 27% of the patients in the TPF arm of the trial did not receive the treatment as scheduled compared to 6% in the arm with concurrent RT-CHX without any induction. Results were reported as intent to treat and per protocol analysis. For the current meta-analysis intent to treat results were implemented. TPF before concurrent RT-CHX resulted in no benefit in OS and PFS.

Haddad et al. [14] randomly allocated 145 patients with locally advanced HNSCC either to 3 cycles TPF (docetaxel 75 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 1, and fluorouracil 1000 mg/m^2/24 h on day 1–4) followed by concurrent RT-CHX with weekly carboplatin or weekly docetaxel, or to concurrent RT-CHX with cisplatin. RT (72 Gy) was administered slightly accelerated within 6 weeks using a concomitant boost technique in both arms of the trial. Risk factors were well balanced between the arms of the trial. All randomized patients were included in the intent to treat analysis. Concurrent RT-CHX resulted in slightly better OS and PFS not reaching statistical significance. The trial was designed to accrual of 330 patients, but prematurely closed because of slow accrual.

Paccagnella et al. [16] included 101 ECOG 0–1 patients with stage III–IVM0 HNSCC in a randomized phase II trial comparing 3 cycles of TPF followed by concurrent RT-CHX (70 Gy/35 fractions/7 weeks + cisplatin 20 mg/m^2 and 5-FU 800 mg/m^2 continuous infusion days 1–4 + 43–46) to concurrent RT-CHX as sole treatment. Risk factors were well balanced between groups and exclusions from the intent to treat analysis were plausible. A significantly higher rate of radiologic complete responses, which was the primary endpoint of the trial, was observed in the TPF-arm of the trial (50% vs. 21%). A trend toward improved OS and PFS was observed. Quite promising results prompted the investigators to continue the study as a phase III trial and to keep the already randomized patients in the extended trial. In addition two new treatment arms were opened resulting in a 2 × 2 factorial design. In the new treatment arms cetuximab (400 mg/m^2 1 week before radiotherapy +250 mg/m^2 weekly during radiotherapy) instead of cisplatin and 5-FU was administered concurrently to RT either as sole treatment or after TPF induction therapy. In this re-designed trial another 319 patients were randomized to a total of 421 patients in the 4 arms. The results of the 2 × 2 factorial design were reported separately during the annual ASCO meetings 2013 [23] and 2014 [20]. The final results have not been published as a full manuscript, however, data from the abstract and additional information from ASCO online were sufficient to extract the required data for the meta-analysis. Risk factors were well balanced between groups and exclusions from the intent to treat analysis appear adequate. The reported results indicate no difference in OS nor PFS between the use of cetuximab or cisplatin/5FU for concurrent treatment with RT, whereas a statistically significant improvement in OS and PFS for the use of TPF induction before RT-CHX or RT + cetuximab was observed. The results of subgroup of 258 patients, which received RT-CHX with or without TPF

induction therapy could be included in the current meta-analysis, whereas the results from patients receiving cetuximab were excluded. In the RT-CHX subgroup, TPF induction did not result in a statistically significant trend toward an OS benefit. For PFS the results of the RT-CHX subgroup are pending. Therefore, the results of the extended 4 arm trial could not be included for the endpoint PFS in this meta-analysis. Instead the results of the smaller phase II trial were included for this endpoint.

Further details on the patient populations in the 5 trials are provided in Table 1 and treatment schedules and potential risks of biases are summarized in Table 2.

Published hazard ratios and hazard ratios extracted from available survival curves for OS and PFS were the foundation of the meta-analysis.

Statistical analyses

All analyses were stratified by trial. For analysis, hazard ratios with 95% confidence limits for OS and PFS were derived from the original manuscripts. The hazard ratios for OS and PFS of 2 trials (Paccagnella [16], Takácsi-Nagy [18]) were not stated in the manuscripts and consequently estimated from published survival curves according to the method described by Parmar et al. [24]. The detailed information of the patients at risk during follow up, and the high resolution of the published curves allowed for an accurate reconstruction of all events and censored cases enabling one to estimate the hazard ratio and confidence limits reliably. Data of included studies were combined to estimate the pooled treatment effect (pooled HR) for patients receiving TPF induction CHX followed by concurrent RT-CHX compared to simultaneous RT-CHX. Meta-analyses of the effect sizes were performed by using random effects models based on parameter estimates of log hazard ratios in Cox models and their standard errors with inverse variance weights.

When the estimate of the heterogeneity variable is zero, the random effect model coincides with a fixed effect meta-analysis. Heterogeneity among trials was quantified with Higgins's and Thompson's I^2. I^2 can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error.

Results are presented with forest plots, in which the estimates of the hazard ratios of all single studies and their combined estimate are visualized. Horizontal bars indicate the amount of variation (95% confidence intervals of the parameter estimates).

All analyses were performed using SPSS version 21.

Results

The results of the meta-analysis (Fig. 1) indicate that induction CHX with TPF before RT-CHX does not improve OS when compared to definite RT-CHX without induction. (Hazard Ratio: 1.01, 95% confidence limits (CL) 0.84–1.21, $p = 0.92$; heterogeneity: $I^2 = 0\%$, $p = 0.7$).

The additional provided funnel plot (Fig. 1) showed no evidence for a relevant selection bias.

Induction chemotherapy with TPF also did not statistically significantly improve PFS in the meta-analysis (Fig. 2) compared to definite RT-CHX (Hazard Ratio: 0.91, 95% CL 0.75–1.1, $p = 0.32$; heterogeneity: $I^2 = 0\%$, $p = 0.77$), although a modest trend toward a benefit was observed. The funnel plot (Fig. 2) suggests no evidence for a relevant selection bias.

Discussion

The TAX 323 and TAX 324 trials, available in 2007, examined the central question to identify the best induction CHX regimen to administrate in HNSCC [2,11]. These two trials and later the

Table 1
Patient characteristics with special attention to lower performance status and advanced tumor characteristics.

	ECOG 1 (instead of ECOG 0) ICT + CRT/CRT	Oropharyngeal cancer ICT + CRT/CRT	Other tumor localization ICT + CRT/CRT	T4 tumor stage ICT + CRT/CRT	Other tumor stage ICT + CRT/CRT	N3 ICT + CRT/CRT	Other nodal tumor stage ICT + CRT/CRT
Cohen [19]	12.6%/15.2%	61.3%/55.6%	Oral cavity 15.3%/13.3% Larynx 12.4%/14.8% Other 2.9%/5.2% Unknown 8.0%/11.1%	19.1%/24.6%	T0 0.7%/0% T1 19.9%/12.7% T2 30.9%/26.9% T3 21.3%/23.9%	11%/11.2%	N2 14.7%/11.2% N2a 8.8%/7.5% N2b 43.3%/44.8% N2c 23.5%/25.4%
Takacsi-Nagy [18]	n.n.	61%/52%	Oral cavity 12%/6% Larynx 9%/3% Hypopharynx 18%/39%	70%/76%	T1 0/3% T2 12%/6% T3 18%/15%	12%/9%	N0 15%/3% N1 6%/12% N2 67%/76%
Hitt [15]	69.7%/73.4%	42.6%/42.2%	Oral cavity 21.3%/20.3% Larynx 18.7%/19.5% Hypopharynx 17.4%/18%	76.8%/75%	T0 0%/0.8% T1 0.7%/0.8% T2 11/9.4% T3 11.6%/14.1%	8.4%/12.5%	N0 17.4%/14.8% N1 16.1%/22.7% N2 58.1%/50%
Haddad [14]	33%/33%	56%/55%	Oral cavity 19%/17% Larynx 14%/19% Hypopharynx 11%/9%	23%/25%	T1 6%/8% T2 40%/28% T3 31%/39%	10%/8%	N0 10%/13% N1 9%/5% N2 71%/73%
Ghi [20]	22%/17%	57%/56%	Oral cavity 18.5%/21% Hypopharynx 23.5%/23% Multiple sides 1%/0%	45.5%/39%	Tx 0.5%/1% T1 6%/6% T2 22/17% T3 26%/37%	9%/6.5%	Nx 1%/1.5% N0 10.5%/11% N1 15%/15.5% N2 64.5%/65.5%

Table 2
Characteristics, treatment compared number of patients and risk of bias.

	Trial characteristics	Trial characteristics induction chemotherapy (IC)	Trial characteristics chemoradiotherapy (CRT)	Treatment compared number of patients	Risk of bias: excluded patients
Cohen [19]	Randomized	2 cycles of TPF	DFHX and hyperfractionated radiotherapy (2 × 1.5 Gy/d) → 39/54/75 Gy (3D conformal RT or IMRT)	*n* = 285 site withdraw *n* = 5 IC-CRT: *n* = 142 CRT: *n* = 138	*n* = 12: (withdraw consent: *n* = 6, *n* = 1: ineligible, *n* = 5: site withdrawn)
Takacsi-Nagy [18]	Randomized	2 cycles of TPF	3 × Cis-DDP (d1, 22, 43) 5 × 2 Gy/week → 50/70 Gy ConPas-technique (conformal parotis sparing)	*n* = 63 3 patients died after IC IC-CRT: *n* = 30 CRT: *n* = 33	3 patients did not appear to the first treatment (IC-CRT)
Hitt [15]	Randomized	3 cycles of PF or TPF	3 × Cis-DDP (d1, 22, 43) 5 × 1.8–2.0 Gy/week → 50/70 Gy	*n* = 439 IC (TPF)-CRT: *n* = 155 IC (PF)-CRT: *n* = 156 CRT: *n* = 128 (*n* = 10 did not receive treatment) *n* = 283 (155 + 128) received CRT ± TPF	No patients were excluded, ITT analysis was performed
Haddad [14]	Randomized	3 cycles of TPF	IC-CRT-arm: NR: Docetaxel weekly for 4 weeks Accelerated Boost RT 6 weeks IC-CRT-arm: Carboplatin weekly Daily RT 7 weeks CRT-arm: 2 × Cis-DDP (weekly for 4 weeks) Accelerated boost RT 6 weeks	*N* = 145 IC-CRT: *n* = 70 CRT: *n* = 75	No patients were excluded
Ghi [20]	Randomized	3 cycles of TPF	Cis-DDP 20 mg/sqm d 1–4, 5 FU 800 mg/sqm week 1 and 6 RT: 70 Gy/2 Gy SD Cetuximab 250 mg/sqm weekly	*n* = 421 IC-CRT: *n* = 210 CRT: *n* = 211 *n* = 6 major violation *n* = 258 (129 + 129) received CRT ± TPF	IC-CRT: *n* = 2 (major violation) CRT: *n* = 4 (major violation)

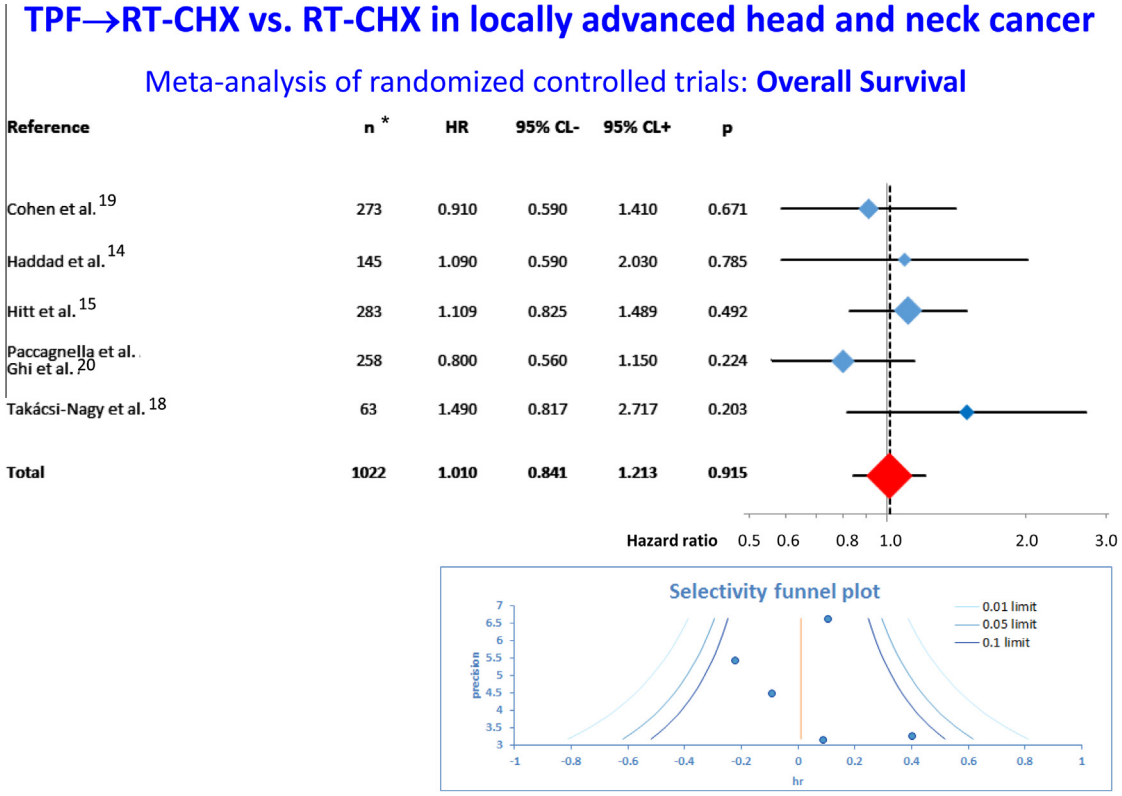

Fig. 1. Meta-analysis of randomized trials. Hazard ratios of induction CHX and concomitant RT-CHX versus RT-CHX alone are given for OS.

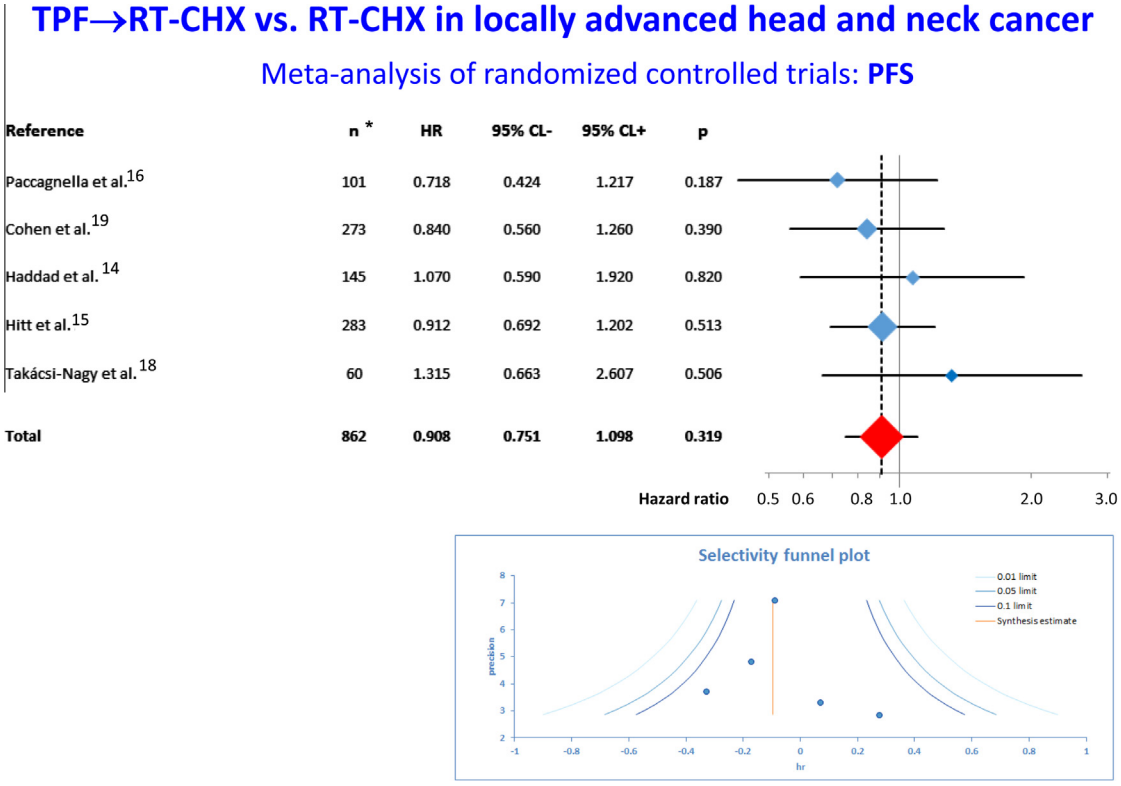

Fig. 2. Meta-analysis of randomized trials. Hazard ratios of induction CHX and concomitant RT-CHX versus RT-CHX alone are given for PFS.

GORTEC laryngeal study indicated that TPF was considerably better than PF for survival, local control, and organ preservation [25]. These investigations established a novel standard of care for induction CHX in the USA and Europe, and resulted in a regulatory approval of TPF for patients with resectable and unresectable HNSCC. Nevertheless, these trials did not answer the important question concerning the relative efficacy of adding induction CHX to RT-CHX compared with RT-CHX alone, the current standard of non-surgical treatment for locoregionally advanced HNSCC.

The results of the presented meta-analysis indicate that induction treatment with TPF before concurrent RT-CHX does not result in a statistical significant improvement of OS or PFS (Figs. 1 and 2). The results of the trials are quite homogeneous and the relatively narrow confidence limits for the cumulative effect size (Hazard Ratio: 1.01, 95% CL: 0.84–1.21) for OS widely exclude a clinical meaningful benefit for the whole group of patients with locally advanced HNSCC. These results are in accordance with a recently published meta-analysis (Zhang et al. [26]) that also detected no significant benefit for induction TPF before concurrent RT-CHX. The trials published by Ghi et al. [20] and Takacsi-Nagy et al. [18] were not included in this work. Instead, a small Chinese trial of unknown quality published in Chinese language was included that also reported no significant advantage from TPF induction. Because of the unknown quality of the data, we decided to exclude this trial.

The results of the Italian trial (Ghi et al. [20]), which reported a significant improvement of OS and PFS associated with TPF induction therapy in locally advanced HNSCC are at first sight in contradiction. However, the benefit in this trial with a 2×2 factorial design was derived mainly from patients who received TPF before RT plus cetuximab, whereas no statistically significant benefit was observed in the subgroup of patients, which underwent RT-CHX after induction TPF. The latter subgroup of patients of this trial was included in the meta-analysis presented here. The observed lack of any benefit from induction TPF seems to be counterintuitive in view of the high rates of tumor responses induced by this treatment. The relative high percentage of patients in all trials, which did not receive concurrent RT-CHX as scheduled could serve as a possible explanation. Nicotine and alcohol abuse induced co-morbidities like arteriosclerosis, coronary artery disease and liver cirrhosis are the same risk factors as for developing head and neck cancer. Induction CHX in these pre-damaged patients is potentially quite toxic and patients may have a high risk not to receive the full dose of RT and concurrent CHX. However, in the trial published by Hitt et al. [15] induction TPF also did not improve survival in the per protocol analysis. The observed small trend toward an improvement in PFS in the TPF arms of the trials but no benefit at all in OS could be related to a higher rate of deaths not related to cancer after TPF induction. Other possible explanations for the lack of benefit from induction TPF include that residual tumor stem cells maybe less sensitive to RT-CHX or proliferate substantially faster than in previously untreated tumors after induction treatment.

The meta-analysis presented here has a number of important limitations. We were unable to assess locoregional tumor control and distant metastasis free survival, since the required information was not available from all trials. The analysis was not based on individual patient's data. Specifically, no information on the outcome by known prognostic factors like T and N-stage, tumor location, HPV/p16-status, ECOG, and smoking habits was available from all trials precluding the possibility of any subgroup analysis. Accordingly, our results do not exclude that induction TPF may improve clinical outcome in important subgroups of patients. In theory, one would expect that patients with better performance status, with HPV/p16 positive tumors or with extensive lymph node involvement may benefit from TPF induction, but data to confirm this hypothesis are lacking. Future trials should aim to investigate the effect of induction TPF separately for HPV/p16 positive and negative HNSCC, since the biology of these variants is very different.

There are several limitations concerning the studies. Whereas the induction chemotherapy regimes differed only slightly, very different concurrent RT-CHX regimes were used. For example the concurrent chemotherapy to RT in the Cohen-trial [19] consists of Docetaxel, Hydroxyurea and 5FU, which is very uncommon. The unexpected good results in the control group of this trial may be correlated with a higher percentage of HPV-positive tumors in the US-study-group.

It is also remarkable and taken into account that the concurrent chemotherapy administered to RT in the Haddad trial [14] is different in the TPF and non-TPF-arm.

Details of the different regimes are shown in Table 2.

The results of the study of Hitt [15] presented in his paper differ from his presentation 4 years ago in the ASCO meeting [27]. In this trial it is also remarkable, that 27% of the patients in the TPF-arm did not receive the treatment as scheduled. This could be a consequence of the relative low experience with TPF in many participating centers, as TPF treatment was quite new at that time.

Similar problems seem to apply for the Ungarian trial (Takacsi-Nagy et al. [18]) in which 3 patients died after induction chemotherapy. A premature closure of the trials was the consequence.

It appears, that TPF should only be used by experienced and specialized institutions.

The trials published by Cohen [20] and Haddad [14] were prematurely closed, because of slow accrual.

The described shortcomings of the included trials limit to some extent the validity of the presented meta-analysis. However, better information is not available for the time being.

Both treatment regimens, concurrent RT-CHX and TPF induction followed by concurrent RT-CHX are effective in the treatment of advanced head and neck cancer patients. In view of the substantial longer overall treatment time associated with induction TPF and the substantial higher rate at least of hematological toxicities, induction TPF cannot be routinely recommended as standard treatment of locally advanced HNSCC.

Conclusion

Our meta-analysis based on data of 5 randomized trials shows that additional induction CHX with TPF before concurrent RT-CHX does not improve OS rate in patients with advanced HNSCC.

Conflict of interest statement

All authors have no disclose of any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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