Chemotherapy in stage III non-small cell lung cancer

Wilfried E.E. Eberhardt[a], Rodrigo Hepp[b]

[a]*Department of Medicine (Cancer Research),* [b]*Department of Radiation Oncology, West German Tumor Centre, University Hospital of University Duisburg-Essen, Essen, Germany*

Introduction

It has recently become clear that stage III non-small cell lung cancer (NSCLC) can be treated with curative intent either by concurrent chemoradiation or combined modality approaches including surgery in well-selected patient populations [1–3]. Nevertheless, the relapse pattern of stage III NSCLC generally indicates that systemic relapse still accounts for about 40% of the first failures following initial curatively intended therapy [4]. Therefore, systemic drug treatment – similar to that in stage II and stage IV disease – will also have to remain an integrated part of the management for these patient groups [5,6]. Cisplatin-based chemotherapy combinations have proven to be systemically effective on micro-metastatic disease of stage III patients in the adjuvant setting following local treatment with surgery [7,8]. Currently, there is no clear evidence for carboplatin-based protocols or non-platinum-containing regimens in contrast to cisplatin-based regimens in these stages [6,9–11]. Even in stage IV, cisplatin-based combinations with newer drugs lead to increased response rates and a clear trend for increased overall survival when directly compared to carboplatin-based combinations [12]. However, it should be noted that combination chemotherapy only exerts a systemic risk reduction-effect on relapses outside the brain and cannot adequately protect the central nervous system [4]. When given in combination with local treatment such as definitive chemoradiation or surgery in stage III NSCLC, two different approaches can potentially be pursued. One is to give a small number of chemotherapy cycles as induction prior to definitive local therapy [13,14], while alternatively the other method tries to give adjuvant chemotherapy as post-local treatment [2,15]. With the most effective cisplatin-based protocols, it has to be stated that no large randomised comparison between these two strategies within trials is currently available. However, single agent consolidation therapy with docetaxel following concurrent chemoradiation did not generate a survival benefit within a randomised trial of the Hoosier Oncology Group (HOG), although the multicentre phase-II pilot of the Southwest Oncology Group (SWOG) had generated encouraging long-term survival data [16]. The probable reason for the ultimate failure of the randomised trial was an increased treatment-related toxicity and toxic death rate in the single agent docetaxel consolidation arm during the pneumonitis phase of the post-radiation setting [17]. Currently, a randomised German trial is looking at consolidation cisplatin and oral vinorelbine versus observation following definitive concurrent chemoradiation [18]. However, it is probably unfair to expect definitive conclusions from this rather small randomised trial alone. In the adjuvant setting of early disease, a meta-analysis of more than 4000 patients was needed to prove a survival benefit of about 5% to 6% with adjuvant chemotherapy at 5 years [8]. When looking at the literature of currently published datasets, the largest and best selected patient group has been that from the chemoradiation arm of the Intergroup Trial 0139 [2]. Treatment was based on a concurrent chemoradiation of two cycles of cisplatin and etoposide together with 61 Gray (Gy) conventionally fractionated radiotherapy. Then, two cycles of consolidation chemotherapy with cisplatin and etoposide were added. A 5-year overall survival rate of 20.3% has been reached in stage IIIA(N2) patients with pathologically proven mediastinal N2-status, representing probably the best survival data so far in a comparable patient population with chemoradiation within a randomised trial. Therefore, at the moment, the two-drug combinations with the largest evidence from randomised trials available in this concurrent chemoradiation setting are cisplatin and etoposide as well as cisplatin and vinorelbine [19]. There are also randomised trials including carboplatin and paclitaxel, but their results should be interpreted with caution as carboplatin lacks clinical data for being a significant radiation sensitiser in stage III (see Table 1) [9,10,20–22]. Furthermore, its systemic efficacy may be significantly inferior to platinum-based protocols on the micro-metastatic disease [12].

Table 1
Prospective multicentre trials of carboplatin-based chemotherapy

Investigators	*N*	Radiotherapy dose	Chemotherapy protocol	LRC 3-year (%)	OS 2-year (%)	Median survival (months)
Clamon et al. [9]	120	60	2 × PV ind	69[a]	10	
CALGB/ECOG	130	60	2 × PV ind + 6 × carb cc	59[a]	13	
Groen et al. [10]	82	60	daily Carb × 6 weeks	40[†]	30[‡]	-
	78	60	RT alone	45[†]	19[‡]	-
Vokes et al. [20]	170	66	2 × CarbT ind + CarT cc	8 mo*	31	14
CALGB	161	66	CarbT cc + 2 × CarbT cons	7 mo*	29	12
Huber et al. [21]	113	60	2 × CarbPac ind	49[‡]	18[ß] ($P = 0.09$)	-
BROCAT	99	60	2 ×CarbT ind + weekly T cc	57[‡]	25[ß]	-
Belani et al. [22]	91	63	2 × CarbT ind	17[ß]	13	
LAMP	74	63	2 × carbT ind + weekly carbT cc	-	15[ß]	12.7
	92	63	weekly carbT cc + 2 × carbT cons	-	17[ß]	16.3

CALGB: Cancer and Leukaemia Group B; ECOG: Eastern Cooperative Oncology Group; LRC: loco-regional control; OS: Overall survival; P: cisplatin; T: paclitaxel; Carb: carboplatin; V: vindesine; cc: concurrent; ind: induction; cons: consolidation.
[a]in-field relapse rate; *progression free survival; [‡]estimated from the survival plots; [†]Overall tumour response; [ß]3-year survival.

There are randomised data from Japan on cisplatin and docetaxel in the concurrent chemoradiation setting and they are quite promising [23]. However, it is not yet clear if the efficacy in Japanese patients can be extrapolated to a Caucasian population. With less toxic chemotherapy drugs only recently available, there has been a renewed interest in the use of consolidation therapy or even maintenance chemotherapy following chemoradiation. Pemetrexed is currently being investigated in a large randomised phase III trial as consolidation in stage III disease but results will probably not be available for a few years. Giving the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) gefitinib as additive treatment following chemoradiation and docetaxel consolidation showed inferior results within a large randomised SWOG trial [24]. It is not clear what impact the docetaxel consolidation eventually had on these findings, but currently this strategy cannot be recommended. Only preliminary data are currently available with vascular endothelial growth factor (VEGF)-acting drugs in the stage III group of patients [25]. With the monoclonal antibody bevacizumab in combination with a chemoradiation protocol, enhanced numbers of pulmonary bleeding and oesophageal toxicity with the development of fistulas have been noted and are currently being critically analysed [25]. Besides, a randomised phase II trial has shown a clear and encouraging signal for an immunotherapy with vaccination against the MUC-antigen in patients with stage IIIB-disease NSCLC [26]. As a consequence, the large randomised START trial is currently recruiting patients with concurrent chemoradiation as the definitive loco-regional treatment. We will have to wait for the results of this pivotal trial until definitive conclusions can be drawn concerning the efficacy of these new immunotherapy principles with vaccination.

Another theoretical possibility would be to investigate the MAGE-A3 vaccination in this setting. Following encouraging results within a randomised phase II trial, this strategy is currently under evaluation in a very large randomised phase III trial in MAGE-A3-positive patients with early disease (IB-IIB) (MAGRIT-TRIAL) [27]. The final results of this trial have to be awaited before further strategies to move this principle into the stage III setting should be considered.

Relapse pattern of stage III

Patients with locally advanced stage III NSCLC can be potentially cured by effective treatment including adequate local control [1,28–31]. This had already been noted with both surgery, in selected groups of stage III (mostly IIIA), and radiation therapy, usually in more advanced IIIA/IIIB. Recently, however, concurrent chemoradiation has become a valid treatment standard for patients with stage III disease considered inoperable by a multidisciplinary treatment team [1,28–32]. One of the lessons of the past can be derived from the large Radiation Therapy Oncology Group (RTOG) database and patterns of

failure of NSCLC patients in stage III [4]. In a joint analysis from several RTOG-trials including radiation therapy alone versus combinations of radiation and chemotherapy, a significant effect of chemotherapy on the site of first failure could be revealed. Significantly less patients showed a systemic relapse outside the brain with chemotherapy included in the treatment. In the patients without chemotherapy the site of first failure was systemic but localised outside the brain in between 33% (squamous cell carcinoma) and 48% (adenocarcinoma). Despite the significant effect of chemotherapy on systemic control outside the brain, the brain relapse rate was not significantly altered by chemotherapy. Thus, combination chemotherapy does not seem to have a prophylactic effect on the development of central nervous system (CNS) metastases and other measures such as prophylactic cranial irradiation have to be actively explored in this setting [33–36]. With the intensification of local control by concurrent chemoradiation plus/minus inclusion of surgery, systemic relapses both inside and outside the brain have become an even more important issue [4,36–40]. Therefore, it seems to be advisable to include an active systemic treatment principle with cisplatin-based chemotherapy with activity on micro-metastatic disease in the treatment protocol. Cisplatin-based combinations have become the standard of care as adjuvant chemotherapy in patients with stage II and stage III disease following complete resection, although the surgical patients in stage III represent a selected subgroup of all stage III patients. Nevertheless, a large meta-analysis in more than 4000 patients has demonstrated that with cisplatin-based chemotherapy, there was a significant 5 to 6% increase in the 5-year overall survival in this situation [8]. Carboplatin-based combinations were only used in one trial, which turned out to be negative, but it did only include patients in stage IB disease [41]. In stage IIIB(wet)/IV, a large meta-analysis based on individual patient data was conducted looking at the effect of cisplatin-based combinations versus carboplatin-based protocols [8]. The analysis showed a significant benefit in the objective response rate for cisplatin-based combinations. The subgroup of patients with cisplatin in a newer third generation protocol showed a significantly improved overall survival in comparison to the carboplatin-based protocols. As a conclusion there are clear indications that cisplatin-based third-generation protocols seem to have significantly higher efficacy on both the macro- as well as the micro-metastatic disease in NSCLC patients. Furthermore, the evidence for a clinical activity of carboplatin as a radiation sensitiser seems to be generally lacking in contrast to cisplatin, even as a single agent [8–11]. Moreover, when looking at the current larger trials in stage III that were based on carboplatin-containing protocols – typically North American trials – the overall survival results of these studies have been generally very disappointing (Table 1) [20,22]. As an ultimate conclusion – despite different preferences in North America – based on the available evidence, cisplatin-based combinations should currently be preferred for both concurrent chemotherapy protocols and systemic treatment in stage III patients where cure is aimed for.

Systemic issues: optimal indications

The preferred group for patients with concurrent chemoradiation in stage III is the one considered inoperable by a multidisciplinary treatment team including a radiation oncologist, a thoracic surgeon, a medical oncologist, as well as a pulmonologist. Patient selection will typically include the majority of patients with pathologically proven or clinically suspected mediastinal N2- or N3-disease or extensive T-involvement of T3- as well as T4-disease [42–45]. Patients will have to have a good ECOG performance status of 0 and 1 prior to treatment start with acceptable comorbidities and no contraindications for aggressive treatment intensification [46]. Selective patients both with IIIA as well as IIIB-disease may be candidates for surgery after induction therapy [47–49]. However, the selection criteria are not well defined and only strict multidisciplinary decisions can try to help improve the identification and selection of these groups (see also the Chapter on Surgery in this Education Book). The North American Intergroup Trial 0139 was based on two prior pilot trials (Table 2) [15,33]. In the first one, selected patients in pathologically proven stage IIIA/N2 and IIIB disease were treated with concurrent chemoradiation with cisplatin/etoposide and 45 Gy radiotherapy [33]. If possible, patients were taken to thoracotomy and completely resected. The 5-year overall survival results of this pilot study were encouraging and recommended a further test of this strategy within a larger randomised trial. The follow-up trial included patients with pathologically proven stage IIIB disease and gave concurrent chemoradiation with two cycles of cisplatin and etoposide to 45 Gy and than a definitive chemoradiation boost to 61 Gy (Table 2) [15]. This concurrent chemoradiation phase was followed by consolidation with two cycles of cisplatin and etoposide. Again, a 5-year overall survival rate of 15% was observed following chemoradiation

Table 2
Table 2 Prospective multicentre trials of concurrent radiotherapy and chemotherapy (CTx) plus consolidation CTx

Investigators	N	Radiotherapy dose	Chemotherapy protocol	Locoregional control		Overall survival	
				3-year S (%)	5-year S (%)	3-year S (%)	5-year S (%)
Albain et al. [15], SWOG 9019	50	61	2 × PE cc 2 × PE cons	NR	NR	17	15
Gandara et al. [16], SWOG 9504	83	61	2 × PE cc 3 × D cons	17 mo*	NR	37	26 mo*
Hanna et al. [17], HOG	73	59.4	2 × PE cc + 3 × D cons	18[a]	NR	27.2 ($P = 0.940$)	NR
	74	59.4	2 × PE cc	26[a]	NR	27.6	NR
Kelly et al. [24]	118	61	2 × PE cc + cons D + Gef	NR	NR	46[†]	26 mo* ($P = 0.013$)
	125	61	2 × PE cc + cons D + Plac	NR	NR	59[†]	35 mo*
Albain et al. [2], INT 0139	194	61	2 × PE cc + cons 2 × PE	NR	11.1[#] ($P = 0.017$)	20.2*	20.3 ($P = 0.24$)
	202	45 + Surg	2 × PE cc + cons 2 × PE	NR	22.4[#]	23.6*	27.2

RT, radiotherapy; CTX, chemotherapy; SWOG, Southwest Oncology Group; HOG, Hoosier Oncology Group; NA, not applicable; NR, not reported; P, cisplatin; E, etoposide; D, docetaxel; cc, concurrent; cons, consolidation; Gef, gefitinib; Plac, placebo; Surg, surgery.
*Median survival; [a]Estimated from the data on sites of relapse or the survival plots; S, survival; [†]2-year survival; [#]progression-free survival.

Table 3
Prospective multicentre phase II trials of induction chemotherapy plus CT/RT

Investigators	N	Radiotherapy dose	Chemotherapy protocol	Locoregional control		Overall survival	
				3-year S (%)	5-year S (%)	3-year S (%)	5-year S (%)
Vokes et al. [13], CALGB	62	66	2 × PG ind + 2 × PG cc	18[a]	NR	28[a]	18.3 mo*
	58	66	2 × PT ind + 2 × PT cc	18[a]	NR	22[a]	14.8 mo*
	55	66	2 × PV ind + 2 × PV cc	18[a]	NR	20[a]	17.7 mo*
Fournel et al. [14], GLOT	63	66	2 × PV cc + 3 × PT cons	NR	8.2 mo*	32	15 mo*
	64	66	3 × PT ind + 2 × PV cc	NR	11.5 mo*	31.6	19 mo*

*Median survival. [a]Estimated from the data on sites of relapse and the survival plots.
RT, radiotherapy; CALGB, Cancer and Leukaemia Group B; GLOT, Groupe Lyon-Saint Etienne d'Oncologie Thoracique; NA, not applicable; NR, not reported; P, cisplatin; T, paclitaxel; Gem, V, vinorelbine; cc, concurrent; ind, induction; S, survival; cons, consolidation.

with consolidation cisplatin and etoposide, quite comparable to the data of the prior trial with tri-modality therapy including surgery. These two pilot trials led to the design of the final phase III trial looking at concurrent chemoradiation followed by surgery versus definitive higher dose concurrent chemoradiation followed by two cycles of consolidation chemotherapy with cisplatin and etoposide [2]. Thus, the cisplatin and etoposide combination currently has the broadest evidence available for inclusion in this setting. One of the advantages of this drug combination seems the fact that it can also be given at full doses of cisplatin as well as etoposide in the concurrent chemoradiation phase to achieve an effect on micro-metastases.

While concurrent chemoradiation followed by consolidation cisplatin-based combination chemotherapy is one possibility to increase systemic control in this setting, other groups have added two or three cycles of induction chemotherapy to concurrent chemoradiation. Table 3 shows the two largest randomised phase II trials with cisplatin-based combinations. The Cancer and Leukaemia Group B (CALGB) trial and the French trial both proved the feasibility of this approach but both cannot give valid final survival results concerning this strategy based on the phase II design [13,14]. In the CALGB trial, a combination of cisplatin and vinorelbine showed the most optimal toxicity profile both in the induction

as well as the concurrent phase [13]. The French trial used two cycles of cisplatin and vinorelbine for the concurrent chemoradiation phase but three cycles of cisplatin and paclitaxel either for the induction or else for the consolidation [14]. The described cisplatin-based chemotherapy protocols were feasible and toxicity was manageable in both studies. With no randomised phase III trials available with the two treatment strategies of induction chemotherapy or consolidation chemotherapy based on a cisplatin-containing combination in this setting, there can be no final recommendation on how to move ahead further (see also the Chapter on Radiotherapy in this Education Book). Probably, individual risk factors of co-morbidity profiles or biological/clinical tumour characteristics may be the most adequate guide for selection to either one of the two strategies in the future, but they have to be defined within prospective trials to generate more evidence on this issue (see also the Chapter on Diagnostic/Staging in this Education Book).

Systemic issues: consolidation

The SWOG carried out a further pilot trial looking at pathologically proven stage IIIB disease in the multicentre setting. Following concurrent chemoradiation with two cycles of cisplatin and etoposide and 61 Gy radiotherapy, three cycles of single agent docetaxel were added as consolidation chemotherapy [16]. The trial was carried out as a large multicentre phase II signal finding study. A median overall survival of 26 months and a 5-year survival rate of 29% turned out to be very encouraging. As a consequence the HOG brought this approach to a randomised trial looking at concurrent chemoradiation with two cycles of cisplatin and etoposide and 60 Gy and added the same three cycles of docetaxel in the experimental arm as consolidation [17] (Table 2). The comparator arm used only the definitive concurrent chemoradiation and gave no consolidation docetaxel. From the initial 243 patients registered to this trial, only 203 patients could be adequately assessed and, finally, only 147 of these were finally randomised in what represents a remarkable selection. However, probably based on the significantly increased toxicities noticed in the docetaxel consolidation phase, the overall survival results in the randomisation turned out to be not significantly different. It has to be noted, that in all the assessed and initially evaluated 203 patients, the 5-year survival was only 10%. The encouraging median survival data in both randomised arms have to be cautiously interpreted on the basis of the above mentioned selection process of 243 patients being accrued but only 147 of them being finally randomised and evaluated for the consolidation effect. Therefore, it seems to be definitely inadequate to conclude from these findings that concurrent chemotherapy of two cycles of cisplatin and etoposide in combination with 60 Gy conventionally fractionated radiotherapy should now be considered the new and valid standard of care for these patient groups. We have to critically accept that the largest group of patients treated with concurrent chemotherapy of cisplatin and etoposide with 61 Gy of radiotherapy was the definitive chemoradiation arm of the North American Intergroup Trial 0139. However, patients in that study received two cycles of consolidation cisplatin and etoposide following the definitive concurrent chemoradiation. The 5-year survival rate of this arm was 20% which probably represents the best long-term survival data observed, so far, within a large multicentre randomised trial setting with an included comparator arm. Therefore, the treatment as described in this definitive chemoradiation arm can be considered to be a standard chemoradiation protocol giving both adequate loco-regional as well as effective systemic control. Consolidation cisplatin and etoposide could be adequately given in more then 75% of the patients in this arm. The toxicity profile of this consolidation therapy with cisplatin and etoposide was, overall, manageable and acceptable. Clearly, consolidation with single agent docetaxel as given in the SWOG pilot and the HOG-randomised trial can no longer be recommended based on the unfavourable toxicity profile and the treatment-related death rate observed in the multicentre randomised study. A probable explanation may be the fact that docetaxel was given exactly during the phase of developing radiation pneumonitis. It might also be that docetaxel can induce serious hypersensitivity reactions and exaggerate pulmonary toxicity or even that it could lead to serious infections which induce bacterial pneumonias by inducing significant neutropenia. The exact mechanism of the observed treatment related deaths on that trial can not currently be given.

New drug combinations

Other groups have used cisplatin-based combinations with newer drugs such as vinorelbine and docetaxel in this concurrent treatment setting. Table 4 shows three trials available on this issue. The Czech randomised trial was a test of sequential versus concurrent

Table 4
Prospective trials of concurrent chemotherapy and radiotherapy with newer drugs

Investigators	N	Radiotherapy dose	Chemotherapy protocol	Time to progression (months)	Median survival (months)	2-year S (%)
Zatloukal et al. [19]	52	60	4 × PV ind + RT	8.5 ($P = 0.024$)	12.9 ($P = 0.023$)	–
	50	60	1 × PV ind + 2 × PV cc + 1PV	11.9	16.6	–
Krzakowski et al. [50]	54	66	2 × PV ind + 2 × PV cc	12.5	23.4	
Kiura et al. [23]	101	60	2 × MVP cc	–	23.7	48.1 ($P = 0.018$)
	99	60	2 × DP cc	–	26.8	60.3

P, cisplatin; T, paclitaxel; D, docetaxel; V, vinorelbine; Vd, vindesine; M, mitomycin; cc, concurrent; ind, induction; S, survival.

chemoradiation [19]. The concurrent arm was based on cisplatin and vinorelbine. This combination and protocol turned out to be feasible and with an acceptable toxicity profile. The concurrent arm also showed better overall survival results. The second study from Poland was a multicentre phase II trial and used two cycles of cisplatin and oral vinorelbine as induction therapy and then two cycles of the same combination as concurrent treatment with 66 Gy of radiotherapy [51]. Toxicity was manageable and overall survival results encouraging. No significant toxicity was observed. The Japanese study combined two cycles of cisplatin and docetaxel with 60 Gy conventionally fractionated radiotherapy [23]. No consolidation or induction therapy was added. This study arm was compared to the "Japanese standard" of two cycles of mitomycin, vindesine, and cisplatin (MVP) given concurrently to the same radiotherapy [32]. Designed as a randomised phase II trial, there was no significant difference between the two arms concerning response rate. Overall survival results turned out significantly better for 2-year survival with cisplatin and docetaxel and there was also a significantly reduced toxicity profile with the newer combination. However, this contrasts to the HOG-group findings with docetaxel and it is not clear whether results from this study in Japanese patients can be easily translated to Caucasian patient populations outside Japan. There are some hints that pharmacogenetic differences between Japanese and Caucasian patients may lead to different toxicity and efficacy profiles following docetaxel treatment. A confirmatory trial of cisplatin and docetaxel in combination with radiotherapy in stage III Western patients has to be awaited prior to more broader treatment recommendations in favour of this regimen. Interestingly there were no increased treatment-related deaths in the docetaxel-based arm in this study.

There are preliminary reports of integrating pemetrexed into definitive chemoradiation protocols as well as the consolidation chemotherapy phase in stage III disease [50,52]. Platinum-based combinations with pemetrexed can be given at full doses in the concurrent treatment phase in combination with radiotherapy, so systemic efficacy should be adequate with no significant dose reductions necessary. In the first randomised phase II trial from CALGB, carboplatin and pemetrexed was given in combination with concurrent radiotherapy and then as consolidation treatment for two cycles [50]. No significant toxicity problems were noted. However, this study looked at the combination of pemetrexed with carboplatin which may be a critical issue in the final interpretation of its results. At the moment, there is a large randomised phase III trial ongoing with a concurrent cisplatin- and pemetrexed-based chemoradiation and then four cycles pemetrexed consolidation versus cisplatin and etoposide in a concurrent chemoradiation protocol followed by "best dealer's choice"-consolidation for two cycles (Fig. 1, data not given here). The patient selection in that study included non-squamous cell histologies only. Results from this and further clinical investigations will be necessary to evaluate this drug both in the concurrent as well as the consolidation setting keeping in mind that the drug's efficacy has only been proven in the subset of non-squamous cell carcinoma patients.

Another large randomised trial has looked at consolidation with the oral EGFR TKI gefitinib versus placebo in stage III patients [24]. Patients received the SWOG regimen with concurrent chemoradiation based on cisplatin and etoposide followed by three cycles of docetaxel consolidation. Patients without disease progression were then randomised into continuous treatment with gefitinib versus placebo (Table 2). Unfortunately, the trial had to be stopped early following an interim analysis demonstrating inferior survival results with the EGFR TKI. It is not clear whether the consolidation docetaxel did have an impact on this negative finding or whether toxicity issues with an EGFR inhibitor in the phase of post

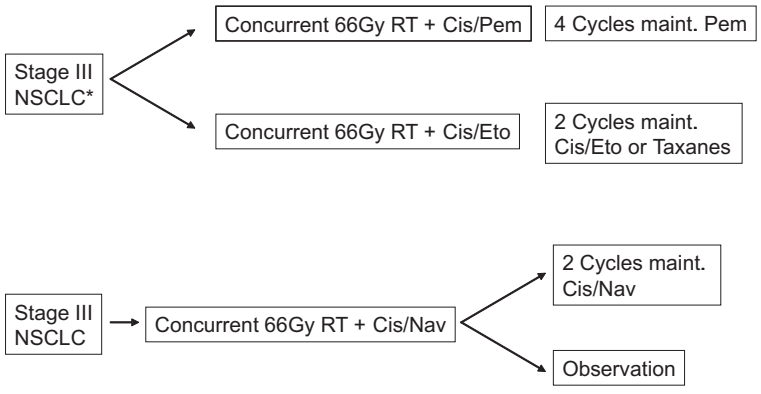

Fig. 1. Currently ongoing randomised studies with consolidation chemotherapy. NSCLC, non-small cell lung cancer; Cis, cisplatin; Pem, pemetrexed; maint, maintenance; Eto, etoposide; Nav, vinorelbine. *Non-squamous cell carcinomas.

radiation pneumonitis could be an explanation for these findings. Another critical argument of that trial was the trials population being unselected both from the clinical point of view (adenocarcinomas, women, never-smokers) and the molecular pathological point of view (EGFR mutations). Recently, there have been reports of a significant additive effect of the monoclonal antibody cetuximab in combination with chemotherapy in advanced disease [53]. First investigations by RTOG are currently looking at adding cetuximab to chemoradiation and a consolidation schema in locally advanced NSCLC [54]. Another new treatment principle, the monoclonal antibody against VEGF, bevacizumab, has been investigated within a phase I/II trial by ECOG in a definitive chemoradiation protocol [25]. Only preliminary data have been reported, but there has been a note of caution concerning serious toxicities such as the development of haemoptysis or fistula to the trachea and the mediastinum with concurrent application of bevacizumab and radiation. Further safety data and a histopathologically stratified toxicity analysis have to be awaited before definitive conclusions can be drawn from these preliminary findings.

Maintenance issues

Maintenance therapy describes the prolonged treatment of one component of the systemic therapy that has also been a component from the initial start of therapy. With the typical long-term toxicities induced by conventional cytotoxic drugs this strategy had been difficult if not impossible to achieve. Only with low-toxicity agents such as pemetrexed available, this treatment approach has only recently been revisited even in advanced NSCLC in stages IIIB and IV [55]. Based on the current findings, it could be an interesting strategy to test this approach of maintenance pemetrexed in adequate histopathologies (non-squamous) in stage III following combined-modality treatment. Toxicity issues may not be that relevant with pemetrexed in comparison to the ones observed with docetaxel in the phase of post-chemoradiation pneumonitis, as far as initial toxicity analyses have demonstrated [51,52].

Immunotherapy in stage III

A randomised phase II trials has been reported looking at a new treatment principle of vaccination against the MUC1-antigen. MUC1 is expressed on a number of epithelial cancers, namely also in NSCLC. A prospective randomised phase II signal finding study showed a significant benefit with a vaccine application against MUC1 in a subgroup of stage IIIB patients following chemoradiation [26]. Based on these encouraging data from the randomised phase II trial, a prospectively randomised phase III study has been launched looking at the administration of vaccine versus placebo in patients following a definitive concurrent chemoradiation protocol. The START trial is open for accrual and final results will not be available for at least one or two years.

Another immunological treatment principle currently under investigation is the vaccination against MAGE-A3 antigen. In patients with MAGE-A3-positive tumours, a signal finding randomised phase II study has generated encouraging results with the adjuvant application of the vaccine over more than 2 years [27]. This study has led to a large randomised phase III trial in early disease after complete resection +/– adjuvant chemotherapy. The plan is for more than 3300 patients to be randomised within the next few years into adjuvant immunotherapy versus placebo.

These results have to be awaited, however, prior to possibly integrating this treatment principle into the management of the stage III disease patient group, but interest in this issue has been generated.

Toxicity issues

With cisplatin-based protocols being the preferred partner both in concurrent chemoradiation protocols and in the consolidation chemotherapy setting, toxicity issues come up for the compliance and toxicity profile observed with these intensive treatments. When cisplatin is split up into 50 mg/m^2 on day 1 and 8 of a cycle, gastrointestinal as well as renal toxicities can be considerably minimised. Supportive measures such as adequate antiemetic treatment and prophylactic hyperalimentation with oral diets can considerably improve the treatment compatibility and compliance.

Cisplatin and vinorelbine has become a typical combination protocol in the adjuvant chemotherapy of early disease or in selected patients with stage III disease after complete resection. Outpatient application is easy and side effects are manageable and mild. Oesophagitis of concurrent chemoradiation seems to have been further reduced by new radiation treatment planning techniques as well as in protocols using cisplatin and vinorelbine for concurrent application.

The combination of cisplatin and etoposide remains a valid standard in these stages but seems to have slightly more oesophageal side effects due to the mucositis seen with etoposide. Pulmonary toxicities of combining chemotherapy and radiotherapy have to be acknowledged and cautiously included into the clinical decision making process [56]. Large patient groups have received both concurrent as well as consolidation application with this combination, thereby representing a valid background for a more generalised treatment recommendation in this setting. The typical co-morbidity profile of a considerable number of patients with locally advanced stage III NSCLC with chronic obstructive pulmonary disease (COPD), coronary heart disease, or diabetes mellitus makes an individualised treatment decision in this stage necessary [46]. Older patients with considerable co-morbidities may not be the ideal patients for treatment intensification. However, age alone should not be the only driving factor, as sometimes "biological age" markedly differs from numerical age and this fact has to be acknowledged [57]. A standard evaluation within a multidisciplinary team seems to be the most optimal procedure to define individualised patient approaches, especially those including surgery or intensified chemoradiation protocols. Lung function, cardiovascular risk factors and significant other co-morbidities should be openly discussed within the group and the individual treatment risks should also be made transparent to the patient so as to include him in the process of decision making. With the increased benefits of the newer treatment planning techniques for radiation therapy, toxicities within these intensified protocols have been remarkably reduced and this again has made inclusion of concurrent chemotherapy or newer drugs much more feasible.

Conclusion

In stage III NSCLC, combination chemotherapy should remain a backbone of treatment due to the high systemic risks of this patient group with nearly 40% of the patients developing systemic failures outside the brain. The broadest evidence is currently available for cisplatin-based combinations, namely cisplatin and etoposide as well as cisplatin and vinorelbine. Carboplatin-combinations cannot be considered to be advisable based on clear evidence from available clinical data, clinical studies or meta-analyses.

A standard and typical treatment approach can be the definitive concurrent chemoradiation arm of Intergroup trial 0139 as large patient groups have been treated with this protocol within an adequate multicentre trial setting. Toxicities of this concurrent chemoradiation and PE-consolidation arm were mild and manageable. Overall treatment results were encouraging with a 20% 5-year survival rate in an adequately selected and well staged patient population making this treatment a potentially curative one.

Consolidation therapy with single agent docetaxel has revealed to be too toxic and not indicated in stage III NSCLC patients after definitive chemoradiation.

Surgery remains an issue following the Intergroup trial in selected patients with pathologically proven stage IIIA(N2) and is probably best identified in a multidisciplinary evaluation. If surgery is included, lobectomy should be the preferred choice and pneumonectomy avoided.

Generally, too few prospectively randomised trials are being performed in stage III disease, so therapists should be encouraged to put patients into ongoing trials. Recent investigations with innovative treatments in randomised clinical trials include vaccination strategies against the MUC-1 antigen, the MAGE-A3-antigen and consolidation treatment with prolonged pemetrexed following definitive chemoradiation in

patients with non-squamous cell carcinomas. Further evidence has to be generated concerning the different co-morbidity profiles, staging and restaging procedures and also concerning the optimal follow-up of patients based on the individual risks of relapse.

Prospective evaluation of prophylactic cranial irradiation has been performed in a large RTOG-trial but final results have yet to be reported. Management of patients with developing brain metastases has to be optimised in this setting. Further introduction of systemic agents into the stage III NSCLC treatment seems to be necessary. Adequate patient selection for therapy with signal transduction inhibitors seems to be an important issue and needs further consideration. Further systemic principles entering the arena within clinical trials are insulin growth factor (IGF)-1 inhibitors, monoclonal antibodies against EGFR, mTOR-inhibitors and multiple others. Typically, these new agents are combined with conventional chemotherapy. Toxicity issues in combination with either chemotherapy, radiotherapy or surgery have to be carefully evaluated. Translational research studies should be implemented into clinical trial designs to search for prognostic and predictive biological markers for future treatment guidance. Stage III patients should preferably be treated within centres with adequate experience and functioning multidisciplinary treatment teams.

Conflict of interest statement

W.E.E. Eberhardt has received honoraria for advisory board function – MerckSerono, Sanofi-aventis, Astra Zeneca, GSK, Eli Lilly, Pierre Fabre, Roche; speakers bureau – MerckSerono, Sanofiaventis, AstraZeneca, GSK, Eli Lilly, Pierre Fabre, Roche. Dr Hepp has no conflict of interest.

References

1 Curran W, Scott C, Langer C. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III NSCLC: RTOG 9410. *J Clin Oncol* 2003;**22**:(abstract 2499).

2 Albain KS, Swann RS, Rusch VA, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer. *Lancet* 2009.

3 Thomas M, Rübe C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008;**9**(7):636–48.

4 Cox JD, Scott CB, Byhardt RW, et al. Addition of chemotherapy to radiation therapy alters failure patterns by cell type within non-small cell carcinoma of lung (NSCCL): analysis of radiation therapy oncology group (RTOG) trials. *Int J Radiat Oncol Biol Phys* 1999;**43**(3):505–9.

5 NSCLC Meta-Analysis Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol* 2008;**26**:4517–26.

6 Aupérin A, Le Péchoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;**17**:473–83.

7 Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;**350**(4):351–60.

8 Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008;**26**(21):3552–9.

9 Clamon G, Herndon J, Cooper R, et al. Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999;**17**:4–11.

10 Groen H, van der Leest AH, Fokkema E, et al. Continuously infused carboplatin used as radiosensitizer in locally unresectable non-small-cell lung cancer: a multicenter phase III study. *Ann Oncol* 2004;**15**:427–32.

11 Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;**326**:524–30.

12 Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in the first-line treatment of advanced non-small cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst* 2007;**99**:847–57.

13 Vokes EE, Herndon JE 2nd, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiation for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002;**20**:4191–8.

14 Fournel P, Vernengegre A, Robinet G, et al. Induction or consolidation chemotherapy with cisplatin and paclitaxel plus concurrent chemoradiation with carboplatin and vinorelbine for unresectable non-small cell lung cancer patients: Randomized phase-II trial GFPC-GLOT-IFCT 02–01. *J Clin Oncol* 2006;**24**:(abstract 7048).

15 Albain KS, Crowley JJ, Turrisi AT, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol* 2002;**20**:3454–60.

16 Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiation in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003;**21**:2004–10.

17 Hanna NH, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008;**26**:5755–60.

18 Beckmann G, Fietkau R, Huber RM, et al. Oral vinorelbine and cisplatin with concomitant radiotherapy in stage III non-small cell lung cancer (NSCLC): a feasibility study. *Onkologie* 2006;**29**(4):137–42.

19 Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiation with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004;**46**:87–98.

20 Vokes EE, Herndon JE 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiation compared with chemoradiation alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol* 2007;**25**:1698–704.

21 Huber RM, Flentje M, Schmidt M, et al. Simultaneous chemoradiation compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. *J Clin Oncol* 2006;**24**:4397–404.

22 Belani CP, Choy H, Bonomi P, et al. Combined chemoradiation regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005;**23**(25):5883–91.

23 Kiura K, Takigawa Y, Segawa H, et al. Randomized phase III trial of docetaxel and cisplatin combination chemotherapy versus mitomycin, vindesine and cisplatin combination chemotherapy with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer: OLSCSG 0007. *J Clin Oncol* 2008; **26**:(abstract 7515).

24 Kelly K, Natale R, Wade J, et al. Phase-III trial of maintanance gefitinib or placebo after concurrent chemoradiation and docetaxel consolidation in inoperable stage III non-small cell lung cancer. SWOG S0023. *J Clin Oncol* 2008;**26**:2450–6.

25 Socinski MA, Morris DE, Stinchcombe TE, et al. Incorporation of bevacizumab and erlotinib with induction and concurrent carboplatin and paclitaxel and 74 Gy of thoracic radiotherapy in stage III non-small cell lung cancer. *J Clin Oncol* 2008;**26**: (abstract 7517).

26 Butts C, Murray N, Maksymiuk A, et al. Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer. *J Clin Oncol* 2005;**23**(27):6674–81.

27 Vansteenkiste J, Zielinski M, Dahabre J, et al. Multi-center, double-blind, randomized, placebo-controlled phase II study to assess the efficacy of recombinant MAGE-A3 vaccine as adjuvant therapy in stage IB/II MAGE-A3-positive, completely resected, non-small cell lung cancer (NSCLC). *J Clin Oncol* 2006;**24**:(abstract 7019).

28 Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;**111**:1710–7.

29 Stinchcombe TE, Fried D, Morris DE, Socinski MA. Combined modality therapy for stage III non-small cell lung cancer. *The Oncologist* 2006;**11**:809–23.

30 Eberhardt, W, Poettgen C, Stuschke M. Chemoradiation paradigm for the treatment of lung cancer. *Nat Clin Pract Oncol* 2006;**3**:188–99.

31 Robinson LA, Ruckdeschel JC, Wagner H Jr, et al. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;**132**(3 Suppl):243S–265S.

32 Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;**17**:2692–9.

33 Albain KS, Rush VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group Phase II Study 8805. *J Clin Oncol* 1995;**13**:1880–92.

34 Eberhardt W, Wilke H, Stamatis G, et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small cell lung cancer: mature results of a phase II trial. *J Clin Oncol* 1998;**16**:622–34.

35 Stuschke M, Eberhardt W, Poettgen C, et al. Prophylactic cranial irradiation in locally advanced non-small-cell lung cancer after multimodality treatment: long term follow-up and investigations of late neuropsychologic effects. *J Clin Oncol* 1999;**17**:2700–9.

36 Andre F, Grunenwald D, Pujol JL, et al. Patterns of relapse of N2 non-small-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? *Cancer* 2001;**91**:2394–400.

37 Poettgen C, Eberhardt W, Grannass A, et al. Prophylactic cranial irradiation in operable stage IIIA non small-cell lung cancer treated with neoadjuvant chemoradiation: results from a German multicenter randomized trial. *J Clin Oncol* 2007;**25**(31):4987–92.

38 Robnett TJ, Machtay M, Stevenson JP, et al. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung cancer. *J Clin Oncol* 2001; **19**:1344–9.

39 Gaspar LE, Chansky K, Albain KS, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol* 2005;**23**(13):2955–61.

40 Gore EM, Bae K, Wong S, et al. A phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small cell lung cancer: Initial analysis of Radiation Therapy Oncology Group 0214. *J Clin Oncol* 2009; **27**:15s, (abstract 7506)

41 Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;**26**(31):5043–51.

42 Rami-Porta R, Ball D, Crowley J, et al. International Staging Committee. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;**2**(7):593–602.

43 Rusch VW, Crowley J, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;**2**(7):603–12.

44 Sculier JP, Chansky K, Crowley JJ, et al. International Staging Committee and Participating Institutions. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol* 2008;**3**:457–66.

45 Vansteenkiste JF, Stroobants SS. PET scan in lung cancer: current recommendations and innovation. *J Thorac Oncol* 2006;**1**:71–3.

46 Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.

47 Redina EA, Venuta F, De Giacomo T, et al. Induction chemotherapy for centrally located non-small cell lung cancer. *J Thorac Cardiovasc Surg* 1999;**117**:225–33.

48 Stamatis G, Eberhardt W, Stueben G, et al. Preoperative chemoradiation and surgery for selected non-small cell lung cancer IIIB subgroups: long-term results. *Ann Thorac Surg* 1999;**68**:1144–9.
49 Grunenwald DH, Andre F, Le PC, et al. Benefit of surgery after chemoradiation in stage IIIB (T4 and/or N3) non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2001;**122**:796–802.
50 Krzakowski M, Provencio M, Utracka-Hutka B, et al. Oral vinorelbine and cisplatin as induction chemotherapy and concomitant chemo-radiotherapy in stage III non-small cell lung cancer: final results of an international phase II trial. *J Thorac Oncol* 2008;**3**(9):994–1002.
51 Heinzerling JH, Hughes RS, Govindan R, et al. A phase I study of pemetrexed plus carboplatin or cisplatin with concurrent chest radiation therapy (CRT) for patients with locally advanced non-small cell lung cancer (LANSCLC). *J Clin Oncol* 2009;**27**:15s (abstract 7545).
52 Govindan R, Bogart J, Wang X, et al. Phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small cell lung cancer: CALGB 30407. *J Clin Oncol* 2009; 27:15 (abstract 7505)
53 Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009;**373**(9674):1525–31.
54 Blumenschein GR, Paulus R, Curran WJ, et al. A phase-II study with chemoriadation in patients with stage IIIA/B non-small cell lung cancer: A report of 2-year and median survival for the RTOG 0324 trial. *J Clin Oncol* 2008;**26**:(abstract 7516).
55 Belani CP, Brodowicz T, Ciuleanu T, et al. Maintenance pemetrexed (Pem) plus best supportive care (BSC) versus placebo (Plac) plus BSC: A randomized phase III study in advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2009;**27**(suppl):15s (abstr CRA8000).
56 Gopal R, Starkshall G, Tucker SL, et al. Effects of radiotherapy and chemotherapy on lung function in patients with non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;**56**:114–20.
57 Langer C, Curran WJ, Komaki R, et al. Elderly patients with locally advanced non-small cell lung cancer benefit from combined modality: secondary analysis of Radiation Therapy Oncology Group 94-10. *J Clin Oncol* 2002;**21**:(abstract 1193).