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European Journal of Cancer 38 (2002) 292–299

European Journal of Cancer

www.ejconline.com

Use of chemo-radiotherapy in locally advanced non-small cell lung cancer

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Received 24 July 2001; accepted 29 August 2001

Abstract

Lung cancer is the leading cause of cancer mortality in the Western countries for both men and women. Approximately 40% of patients present with locally advanced and/or unresectable disease. While small improvements in outcome have occurred for this group of patients in the last decade, 5-year survival remains low, ranging from 5 to 20%. Distant metastases and loco-regional progression remain significant patterns of failure. Up to the late 1980s, the standard management for locally advanced non-small cell lung cancer (NSCLC) was conventional thoracic radiotherapy, but when treated with radiotherapy alone, less than 10% of patients survived for 5 years or more. 60–70% failed at distant sites and less than 20% achieved durable local control. The addition of chemotherapy reduces the rate of distant failure, improves survival and the combination of chemotherapy and radiotherapy has become the standard of care of patients with locally advanced NSCLC. Current developments aim to optimise individual components of combined modality schedules, increase their synergism and minimise toxicity. © 2002 Published by Elsevier Science Ltd.

Keywords: Chemotherapy; Radiotherapy; Non-small cell lung cancer

1. Introduction

In the United States, lung cancer is the third most common cancer after prostate and breast cancer, but it is the leading cause of cancer death both in men and women [1]. Surgery is the main curative treatment for early stage non-small cell lung cancer (NSCLC), i.e. clinical stages I and II, but most patients with NSCLC have advanced disease at the time of presentation and are not candidates for curative surgery. Approximately a quarter of patients with NSCLC present with locally advanced (clinical stage III) disease and, even if the tumour appears confined to the chest, it is none the less too extensive to warrant surgical resection. The classification of stage III category was reviewed in 1997, but it still remains heterogeneous: it includes a prognostic spectrum of subgroups ranging from T3 lesions with a single involved hilar (N1) node to a large primary tumour that invades the contralateral mediastinum and supraclavicular lymph nodes (N3) and/or a malignant pleural effusion (T4) [2]. Considering all the potential presentations, there are multiple treatment approaches available for these patients. The T3N1 group is usually treated with primary surgery, while pre- or post-operative chemotherapy and/or radiation may be considered as adjuvant treatments. Patients with malignant pleural effusion are routinely considered as those with stage IV disease [3]. Their treatment approach is palliative, although the 1986 Union International Contre le Cancer (UICC) classification relocated them from stage IV to stage IIIB.

Up to the mid-1980s, for most patients with locally advanced NSCLC, the standard management was conventional external beam thoracic radiotherapy alone, delivered at a dose of 60 Gy over 6 weeks, with a classical fractionation of 1.8–2 Gy per day. However, the results of radiotherapy alone were very disappointing, with a median survival time of less than 1 year and 2- and 5-year survival rates of approximately 15 and 5%, respectively [4]. In a study delivering up to 70 Gy, Hazuka and colleagues reported local tumour progression as the first site of failure in 50% of patients [5]. These poor results in such a common disease have led towards a greater intensification of local therapy

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0959-8049/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0959-8049(01)00359-8

through the use of altered fractionation schemes, three-dimensional conformal thoracic radiotherapy (TRT), radiosensitisers as well as attempts to develop chemotherapy schedules in combination with standard or altered fractionation schemes. However, while local therapy will have no influence on survival if cells resistant to chemotherapy have escaped from the primary site, local control is still a prerequisite for cure. Indeed, failure pattern analyses in NSCLC demonstrate that both locally persistent (or recurrent) disease and metastases are significant problems [6]. We will present here the state of the art and the perspectives of these two modalities in locally advanced NSCLC.

2. Radiotherapy

Recent efforts to escalate the total radiation dose to improve local control and survival have been reported using multiple daily fractions of radiotherapy either through hyperfractionation, accelerated fractionation or Continuous Hyperfractionated Accelerated Radiotherapy (CHART).

Hyperfractionation includes a decreased dose per fraction (typically 1.0–1.2 Gy), an increased number of fractions and a conventional overall treatment time. The goal of hyperfractionation is the differential sparing of late-reacting normal tissues (lung, spinal cord, heart), resulting in a reduction of chronic toxicity. Tumours tend to have a slower repair rate than normal tissues, so that multiple daily doses, may provide considerable therapeutic advantage over conventional once daily fractionation schedules. In these multiple daily fraction approaches, two fractions per day are typically used, with an interval between fractions of 6–8 h to allow for repair of radiation-induced sublethal damage in normal tissues.

A large Radiation Therapy Oncology Group (RTOG) phase II study aimed to optimise total radiation dose with an hyperfractionated schedule to test total doses between 62 Gy and 79.2 Gy fractions of 1.2 Gy, administered twice daily. A dose–response relationship was observed, but the greatest benefit was seen with a dose of 69.6 Gy with 1 and 3-year survival rates of 58 and 20%, respectively [7].

The rationale for accelerated hyperfractionation is to exploit the potential benefits of both accelerated fractionation (fractions virtually the same as those administered with the classical continuous schedule, given several times per day with a considerable shortening of the total treatment time, decreasing in this way the opportunity for repopulation of tumour cells during treatment, but usually associated with severe acute reactions of normal tissues) and hyperfractionation. The dose per fraction is reduced (usually 1–1.2 Gy, administered multiple times daily, typically two or three times); the total number of fractions is increased and the overall treatment time is somewhat decreased.

These hyperfractionated studies still leave patients untreated during the weekend. Radiolabelling studies of tumour cell kinetics have shown high potential *in vivo* doubling times in NSCLC. This has led to the development of CHART in which all treatment is compressed into 12 consecutive days by giving three fractions of 1.5 Gy/day at 6-h intervals for a total of 54 Gy, patients being also treated during the weekend.

A randomised clinical trial compared CHART with conventional radiotherapy in 563 patients with locally advanced NSCLC [8]. There was a 24% reduction in the risk of death in the CHART group that is equivalent to an absolute improvement in 2-year survival of 9% (from 20 to 29%; $P=0.004$), raising to 14% in squamous cell carcinoma. CHART also improved local control and disease-free survival. A modification of this schema has been developed, in which patients are given the week-end off ('CHART-WEL': CHART weekend less) [9]. Based on the same concept, King and colleagues reported a median survival of 15.3 months in 49 patients who underwent an accelerated regimen with a concurrent boost, to a total dose of 73.6 Gy [10].

With traditional planning, geometric misses of the tumour occur frequently and 3D-CRT (three-dimensional conformal radiotherapy) should be able to significantly reduce this type of error. It is a mode of high precision radiotherapy which accurately conforms the isosurface of a given radiation dose to the anatomical boundaries of the tumour in its entire three-dimensional configuration and has the potential to enhance delivery of high-dose radiation with a reduction of the dose to normal tissues. Pivotal studies exploring the feasibility of this technique showed that the delivery of up to 102.9 Gy is safe with predictable toxicity and promising results in terms of survival [11].

3. Chemotherapy

The value of adding radiotherapy to chemotherapy in stage III NSCLC has been assessed in a randomised study by Kubota and colleagues [12]. In this study, after two cycles of chemotherapy, patients with locally advanced disease were randomised to receive thoracic radiation or not. There were different chemotherapy regimens: (i) cisplatin 100 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1, 8 and 15; (ii) cisplatin 80 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1 and 8, mitomycin-C 8 mg/m^2 day 1; (iii) cisplatin 80 mg/m^2 on day 1, etoposide 100 mg/m^2 on days 2, 4 and 6, vindesine 3 mg/m^2 on days 22 and 29; mitomycin-C 8 mg/m^2 on day 22. RT consisted of 50–60 Gy in 25–30 fractions. 63 patients were enrolled and were evaluable. Median survival times were similar for the two groups (461 days in

the CT/RT group and 447 days in the CT alone group). The survival rate was 36% at 2 years, and 29% at 3 years in the CT/RT group compared with 9, and 3% respectively, in the CT alone group ($P=0.016$ and 0.0049). It was concluded that, in locally advanced NSCLC, cisplatin-based chemotherapy followed by chest radiation significantly increases the number of long-term survivors compared with chemotherapy alone.

4. Combined chemoradiotherapy regimens

There are three major modalities of combining radiation and chemotherapy: (a) *sequential*, in which one modality is completed prior to the start of the other; (b) *concurrent*, where radiation and chemotherapy are given on the same days; and (c) *alternating*, in which courses of radiation and chemotherapy are alternated so that administration of the two modalities is completed over the same overall time period without concurrent administration [13].

Historically, the sequential trials were firstly completed and two major points were observed: (i) the response rate of patients with stage III NSCLC to a variety of cisplatin-containing regimens given for two or three cycles before TRT was in the range of 30–50%, and (ii) progression within the thorax during chemotherapy was quite uncommon. An initial chemotherapy programme should shrink the tumour and consequently the radiation treatment would be more effective against the smaller, potentially better oxygenated, residual tumour. Among 11 randomised trials of sequential chemo-radiotherapy versus radiation therapy alone, six demonstrated the superiority of the combined treatment. In the CALGB study, patients were randomised to either a standard 60Gy radiation treatment administered over 6 weeks, or two cycles of chemotherapy (vinblastine/cisplatin) followed by the same radiation. The authors reported a significant improvement favouring the chemoradiotherapy arm, for median survival time (13.7 versus 9.6 months), 5-year (17% versus 7%) and 7-year survival (13% versus 6%) respectively [14,15]. In a confirmatory study led by the RTOG, patients were randomised to radiotherapy alone (60 Gy) versus two cycles of cisplatin/vinblastine followed by standard radiotherapy at the same dose versus hyperfractionated radiotherapy (69.6 Gy) [16]. This trial confirmed the improvement of median survival for the combined arm (13.7 months versus 11.6 for the radiotherapy alone), while the arm with hyperfractionated radiotherapy did not show a significant superiority over standard RT. In parallel with the CALGB work, French investigators performed a multicentre study (CEBI 138) with 353 patients using a sandwich regimen with induction and post-radiotherapy chemotherapy (cisplatin/lomustine/vindesine/cyclophosphamide) compared with RT alone (65 Gy over 6 weeks): median survival was 12 months for the combined arm compared with 10 months with radiotherapy alone; a survival advantage was described in favour of the combined treatment (20 versus 12% at 2 years, $P=0.02$) [17]. In this study, local persistence or local failure after complete response occurred in over 80% of patients in both arms, without any statistical difference between the two arms. In the arm with the addition of chemotherapy, there was a reduction in the distant metastasis rate from 65 to 45% with the addition of chemotherapy ($P<0.001$) responsible for the survival benefit [18].

While there are some negative trials with combined modality therapy compared with radiotherapy alone, the individual data based meta-analysis performed in 1994 reported a modest, but significant, advantage of 2% in survival at 5 years with the sequential combination of CT and RT compared with RT alone in a total of 3033 patients [19].

There are numerous biological arguments to give both modalities concurrently. Accelerated repopulation of tumour can occur after chemotherapy, despite apparent complete remission. Delays in starting radiotherapy after induction chemotherapy, mainly related to a slow recovery from the effects of chemotherapy or to a lack of compliance, may allow tumour repopulation a head-start on radiotherapy [20]. A simultaneous administration of chemotherapy and RT takes advantage of tumour cell killing and radiosensitisation by chemotherapy [21]. However, the disadvantage of concurrent chemo-radiotherapy is the increased risk of acute toxicity because chemotherapy may inhibit the repair of radiotherapy-induced sublethal damage in normal tissues, as well as in the tumour. The challenge is to balance the improved efficacy and the increased toxicity. Some trials have been reported with single-arm concurrent chemo-radiotherapy. In one of these, concurrent cisplatin, oral etoposide and hyperfractionated radiation showed a median survival time 2-year survival rate of 18.9 months and 35%, respectively [22].

In a randomised trial, the European Organization for Research and Treatment of Cancer (EORTC) showed a significant survival advantage for low-dose daily cisplatin with concomitant radiotherapy compared with radiotherapy alone (3-year survival rate: 16% versus 2%) [23]. Furuse and colleagues reported a 2-year survival rate and median survival time of 36.7% and 16 months with combined mitomycin-C, vindesine plus cisplatin, and split-course radiotherapy [24]. In a phase II study of concurrent radiotherapy and chemotherapy with cisplatin plus vindesine, the objective tumour response rate (74.3%), median survival (14.8 months), and 2-, 3- and 5-year survival rates (30.3, 21.5 and 14.8%, respectively) were comparable to the results of similar other trials [25].

In another study by Jeremic and colleagues, the patient population was randomised between hyperfractionated radiotherapy alone (1.2 Gy twice daily to a total dose of 64.8 Gy) and two combinations of hyperfractionated radiotherapy plus concurrent carboplatin/etoposide, administered weekly or every other week [26]. In this trial, median survival times were 8, 18 and 13 months, respectively, and 3-year survival rates were 7, 23 and 16%, respectively ($P = 0.027$).

However, the CALGB study did not demonstrate any benefit of the addition of weekly carboplatin to radiation after induction therapy with cisplatin and vinblastine [27].

Finally, a recent Japanese randomised study reported an advantage for concurrent versus sequential chemoradiation in 320 patients with unresectable stage III NSCLC treated with mitomycin-C, vindesine and cisplatin, given either concurrently with or prior to thoracic radiation [28]. The overall response rate was significantly superior for the concurrent schedule (84% versus 66.4%) as was the median survival time (16.5 versus 13.3 months) and the 3- and 5-year survival rates (27% versus 12.5% and 15.8% versus 8.9%, respectively) [29]. These results have been recently confirmed by the RTOG 94-10 trial, in which 611 patients were randomised to receive induction chemotherapy (cisplatin 100 mg/m^2 and vinblastine 5 mg/m^2) followed by standard radiotherapy (60 Gy) versus the same chemotherapy and concurrent radiation starting on day 1 versus a third arm of hyperfractionated radiotherapy and concomitant cisplatin and oral etoposide [30]. Among the 597 evaluable patients, grade 3–4 non-haematological toxicity was higher in the concomitant treatments rather than the sequential one, but late toxicity was similar and median survival time favoured, although not significantly, the concurrent treatment (17 months versus 14.6 in the sequential arm and 15.6 in the hyperfractionated radiotherapy arm).

5. New drugs

The optimal chemotherapy regimen in the management of inoperable NSCLC is still unknown. Recently, several new chemotherapeutic agents have shown activity in chemotherapy-naive NSCLC and most of these agents have been proven to be *in vitro* potent radiosensitisers. These include paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan. Several phase II studies testing new compounds alone or in combination with cisplatin given concurrently with radiation in locally advanced NSCLC have been reported in recent years.

A series of pilot studies using paclitaxel as a radiosensitising agent were performed in the early 1990s. The first studies recommended a dose of 55 mg/m^2 weekly in combination with simultaneous thoracic radiation for a total dose 59.4 Gy (Table 1). The overall response rate obtained with such combination was 68% among 25 evaluable patients [31].

However, most studies evaluated paclitaxel in combination with platinum compounds (Table 2). In a phase I trial, the combination of weekly paclitaxel and cisplatin was given concurrently with chest radiotherapy. In this pilot study, the authors demonstrated that weekly cisplatin/paclitaxel at 35 and 45 mg/m^2, respectively, can be safely administered in combination with standard thoracic radiation (2 Gy/day), while cisplatin 30 mg/m^2 and paclitaxel 45 mg/m^2 can be administered with hyperfractionated radiotherapy (1.2 Gy twice daily) [32]. In a French study, weekly carboplatin (area under the concentration curve) (AUC) 2) and paclitaxel (40 mg/m^2) were administered throughout thoracic radiotherapy (65 Gy) in patients with locally advanced NSCLC. Among 19 evaluable patients, the response rate was 74% and among a total of 30 patients enrolled, only one episode of grade III oesophagitis was reported [33]. In another study, Belani and colleagues combined weekly paclitaxel (45 mg/m^2 in a 3-h infusion) and carboplatin (100 mg/m^2) with simultaneous thoracic radiotherapy (60–65 Gy) and reported a 3-year survival rate of 54% [34]. Similarly, Choy and colleagues using weekly paclitaxel and carboplatin with concurrent (daily or hyperfractionated) thoracic radiotherapy documented a significant tumour regression in 76% of the cases with a median survival of 20 months [35]. In the study reported by Ratanatharathorn, paclitaxel at the dose of 45 mg/m^2 and carboplatin AUC 2, were administered weekly concomitantly with radiation. Subsequently, 4 weeks after the completion of radiotherapy,

Table 1
Single agent paclitaxel in stage III NSCLC

Reference	Dose		*n*	OR (%)	MS (months)	1 year survival (%)
	Paclitaxel (mg/mq)	RT (Gy)				
[31]	45–65/wk (3 h)×3–7 wk	1.8/d 5×/wk (total 59.4)	25	68	6	NR
[52]	60/wk (3 h)×6 wk	40 + boost (20)	29	81	18.4	61
[53]	25–40/biweekly×6 wk	1.8–2/d 5×/wk (total 61)	25	80	14	>50
[54]	40–80/wk (3 h)×5 wk	2/d 5×/wk×5 wk (total 50)	16	44	NR	NR

OR, overall response rate; NSCLC, non-small cell lung cancer; RT, radiotherapy; wk, week; NR, not recorded; d, day; MS, median survival.

paclitaxel 175 mg/m^2 and carboplatin AUC 6 were given for four cycles. The median overall survival time was 14.5 months, with a median progression-free survival time of 10.5 months; the primary tumour site and/or the chest wall were the first sites of failure in 64.7% of patients [36].

Another feasible approach consists of the administration of 2–3 courses of induction chemotherapy followed by a concomitant chemotherapy approach. The induction treatment with cisplatin 120 mg/m^2 day 1 plus paclitaxel 135 mg/m^2 3-h infusion day 1 plus vinorelbine 30 mg/m^2 days 1, 8 or 15 was tested in a Spanish phase II trial. 31 patients with inoperable stage III disease [37] were enrolled and, when feasible, they received also chemotherapy concurrently at the beginning of the radiation course and in the last week of a hyperfractionated radiotherapy course (69.6 Gy total dose). The response rate was 58% with a median survival time of 16 months. The most common toxicity of chemotherapy was haematological (febrile neutropenia 13%, grade IV neutropenia 42%), while the major toxic effects of radiotherapy were grade II–III oesophagitis and dysphagia, which occurred in 41% of patients.

Langer and colleagues employed two cycles of 3-weekly paclitaxel (175–225 mg/m^2 over 3-h infusion) plus carboplatin (AUC 7.5), followed by thoracic radiotherapy (60 Gy in 2-Gy fractions) starting on day 43 concurrently with paclitaxel and carboplatin chemotherapy on days 43 and 64. The 1-year survival rate was 62% in the first 21 patients accrued in this trial [38].

In a randomised phase II study, Curran and colleagues compared a sequential chemo-radiotherapy versus an induction chemotherapy followed by concurrent chemo-radiotherapy versus a concurrent approach using the carboplatin/paclitaxel combination: the initial report was recently presented and the interim survival results in arms 1 and 3 are sufficiently promising to continue the accrual [39].

A synthetic allosteric modifier of haemoglobin (RSR13) was tested in combination with carboplatin/paclitaxel: 52 patients with stage III NSCLC were treated with two cycles of carboplatin AUC 6 and paclitaxel 225 mg/m^2 followed by RT (64 Gy) with daily RSR13 (75 mg/kg with possible adjustments to 100 or 50 mg/kg). Overall response rate was 87 and 29% of patients experienced one or more episodes of transient RSR13-induced hypoxaemia during the treatment [40].

Vokes and colleagues have recently reported the preliminary results of the randomised phase II CALGB 9431 of gemcitabine or paclitaxel or vinorelbine with cisplatin as induction chemotherapy and concurrent chemoradiotherapy in stage III NSCLC (Table 3). The response rate in all three arms appeared similar, but the gemcitabine/cisplatinum arm showed the highest rate of grade 3–4 thrombocytopenia (53% versus 6% or 0% in the other arms) and oesophagitis (49% versus 31% and

Table 2
Paclitaxel in combination with a platinum compound in stage III NSCLC

Reference	Dose			*n*	OR	MS (months)	1 year survival (%)
	Paclitaxel (mg/mq)	RT (Gy)	Platinum (mg/mq)				
[32]	45/wk	60	30–35/wk[a]	25	60	16	66
[33]	40/wk	65	AUC 2/wk[b]	30	74	NR	NR
[34]	45/wk	60–65	100/wk[b]	38	NR	>36	63
[35]	50/wk	62	AUC 2/wk[b]	37	76	20	56
[36]	45/wk	60	AUC 2/wk[b]	30	77		

RT, radiotherapy; AUC, area under the concentration curve; NSCLC, non-small cell lung cancer; MS, median survival; OR, overall response rate; wk, week; NR, not reported.
[a] Cisplatin.
[b] Carboplatin.

Table 3
CALGB study 9431 [41]

	n	IIIB (%)	Induction CT C1 + C2	Concomitant CT-RT C3 + C4	OR after induction CT (%)	OR after concomitant CT-RT	MS (months)
Vinorelbine + cisplatin[a] *n* = 58	58	62	25 mg/mq d1, 8, 15 C 1d 1, 8 C2	15 mg/mq d1, 8	41	69	17.7
Paclitaxel + cisplatin[a] *n* = 59	59	46	225 mg/mq d1	135 mg/mq d1	32	64	14.7
gemcitabine + cisplatin[a] *n* = 63	63	40	1250 mg/mq d1, 8	600 mg/mq d1, 8	37	70	18.4

d, day; CALGB, Cancer Leukemia Group B; CT, chemotherapy; RT, radiotherapy; OR, overall response rate; MS, median survival; C, cycle.
[a] Cisplatin = 80 mg/mq d1 in all arms.

25% in the other arms). The median survival time for all patients was 18 months, with a 1-year survival rate of 66% (68, 65 and 63% for gemcitabine, vinorelbine and paclitaxel arms, respectively) [41].

Docetaxel is another new compound and its activity leads to the stabilisation of microtubules which blocks mitosis in the G2/M phase, thereby playing a potential role in enhancing the radiosensitivity to ionising radiation. The maximum tolerated dose for docetaxel was 30 mg/m^2 per week×6 given alone with radiotherapy and 20 mg/m^2 per week×6 when associated with carboplatin AUC 2 [42].

Gemcitabine has a great radiosensitising potential, but results in substantial toxicity when combined with radiotherapy. In a phase I trial, six weekly administrations of gemcitabine at 1000 mg/m^2 during thoracic radiation (60 Gy in 2-Gy fractions) resulted in excessive non-haematological toxicity, with serious complications of oesophagitis and pneumonitis in another 3 patients [43]. Even with the use of 3D-radiotherapy, the maximum tolerated dose was 190 mg/m^2 and, although the length of oesophageal exposure was consistently reduced (from 71% for the conventional 2D-radiotherapy, to 11% for the 3D approach), oesophagitis still remained the limiting toxicity [44]. However, in the CALGB 9431 study, 600 mg/m^2 of gemcitabine was administered safely during thoracic radiation when given only on days 1 and 8 of a 3-week cycle. However, the gemcitabine arm was associated with more grade 3 or 4 toxicity during the concurrent radiotherapy than paclitaxel and vinorelbine [41].

Experimental studies have shown that vinorelbine is a powerful radiosensitiser *in vitro*; in a phase I study, Gridelli and colleagues reported the feasibility of the combination of thoracic radiotherapy and concurrent vinorelbine administered daily with a maximum tolerated dose of 4 mg/m^2 [45]. Recently, Garst and colleagues reported the results of a phase II study, in which 36 patients with stage III NSCLC were treated with vinorelbine 5 mg/m^2 three times a week and concomitant RT (66 Gy). The overall response rate was 56% and the median survival was 20.7 months. Grade III oesophagitis was observed in 5 patients (14%) [46].

In a phase II randomised study Zatloukal and colleagues, reported a direct comparison between concomitant and sequential chemo-radiotherapy. Cisplatin and vinorelbine were administered in both arms at the same dose intensities. The concomitant approach resulted in major clinical activity, with an overall response rate of 85% and median survival time of 20.7 months as opposed to 45% and 14.1 months, respectively, for the sequential arm [47].

Irinotecan has also been evaluated and the recommended dose was 60 mg/m^2 on days 1, 8 and 15 plus cisplatin on day 1 of a 28-day cycle given concurrently with a split course of thoracic radiation (50.6 Gy in 2-Gy fractions) [48].

A European study randomised the patients to receive radiotherapy alone versus daily carboplatin (15 mg/m^2) in combination with radiation (66 Gy in 33 fractions over 6 weeks and 3 days), after an induction treatment with cisplatin and vinorelbine. Among the first 190 randomised patients, radiation therapy was fully delivered to 141. Overall toxicity was comparable in both arms. One month after the end of treatment, an objective response was observed in 72% of patients and a stabilisation in 23% [49].

Hypoxic cells are more resistant to radiation because of the radiosensitising effects of oxygen, and also to standard chemotherapy since hypoxic tumours often have poor blood flow. Tirapazamine is an hypoxic cytotoxin with selective toxicity to hypoxic cells [50]. It has been proven to enhance survival in patients with advanced NSCLC when combined with cisplatin when compared with cisplatin alone [51]. It is currently evaluated in association with other drug combinations and with radiation.

6. Conclusions

Future trials will be designed to integrate the optimal local and systemic strategies in locally advanced disease. Treatment strategies to enhance local control, such as altered fractionation or dose escalation with conformal RT, will need to be safely combined with systemic chemotherapy.

The question of the sequencing of both modalities has not been fully resolved, but there are several theoretical and some clinical data encouraging the use of concurrent delivery of radiotherapy and chemotherapy.

At this time, outside of clinical trials, induction chemotherapy followed by TRT should be considered standard treatment for patients with good performance status, unresectable, Stage IIIB NSCLC patients provided they have experienced minimal or no weight loss and they do not have evidence of pleural effusion.

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