Oncology Spectrums
The Journal of Integrated Cancer Medicine

The Contemporary Management of Lung Cancer

Corey J. Langer, MD

- ☐ Diagnosis and Treatment
- ☐ Chemotherapy Guidelines
- ☐ Chemotherapy Regimens

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Dr. Langer is the co-director of thoracic oncology for the Fox Chase Cancer Center in Philadelphia, PA.

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Introduction

Lung cancer remains the leading cause of cancer death in United States (US) men and has become the leading cause of cancer mortality in women over the past 10 years. More patients die of lung cancer than the next three most common causes of cancer death: breast cancer, colorectal cancer and prostate cancer combined. Over 170,000 new cases will be diagnosed in 2001; all but 14% will succumb within five years.[1]

Non-small cell lung cancer (NSCLC) accounts for over 80% of all lung cancer in the US with prognosis and treatment tightly linked to stage.

General Issues in Lung Cancer

A number of unanswered or evolving issues remain in lung cancer. These issues include: revisiting the issue of screening and early detection using spiral computed tomography (CT); the evaluation of new, non-toxic agents for chemoprevention in those at risk and in those with pathologic stage I disease; the role of molecular genetics and other biologic markers in fingerprinting tumors, predicting prognosis and tailoring therapy; the ultimate role of newer agent(s) as part of neoadjuvant therapy in less advanced (stage II and III) disease; the role of newer agents that alter the tumor milieu/microenvironment (eg, angiogenesis or metalloproteinase inhibitors, etc.) in delaying progression in late disease and preventing relapse in earlier disease; the proper sequencing of radiation and chemotherapy in stage III disease (eg, the ultimate role of sequential neoadjuvant and concurrent chemoradiation); the roles of biologics, non-chemotherapeutic radiosensitizers and normal tissue protectants in stage III NSCLC; the optimal dose, volume, fractionation and schedule of radiation therapy (RT), and the role of 3-D conformal RT; and the necessity of surgery after chemoradiation for stage III disease.

Small Cell Lung Cancer

Small cell lung cancer (SCLC) represents 16% to 18% of newly diagnosed lung cancers each year in the US. This incidence, in contrast to NSCLC, may be declining, but the impact is still substantial. The overall incidence is roughly 25,000 to 27,000 patients yearly, of whom one-third are diagnosed with limited, potentially curable disease, and two-thirds have extensive disease. The majority of patients are treated in the community, and the majority, unfortunately, are not candidates for clinical trials.

Headway in the treatment of SCLC will require innovative strategies integrating new agents, particularly biologics. It is questionable if the current treatment paradigm combining conventional chemotherapy and radiation can improve outcome substantially. At this point, however, two issues are clear: (1) concurrent chemoradiation is superior to other approaches in the treatment of limited disease; and (2) prophylactic cranial irradiation at this point, should be considered routinely in the treatment of patients with limited disease, particularly younger patients who have responded to induction therapy or combined modality therapy.

In the setting of chemosensitive relapse, topotecan and CAV yielded therapeutic equivalence with respect to response rate and survival, but symptom relief was superior with topotecan.

Finally, the role of newer agents, such as irinotecan and topotecan, needs to be assessed prospectively and critically before being introduced into the standard treatment paradigm.

Prevention

Primary prevention remains the most crucial path to reducing the pandemic of lung cancer and educating grade schoolers about the lethal effects of cigarettes and other tobacco products is one of the most effective prevention methods we currently posses.

Diagnosis and Treatment

01 Lung Cancer Risks

Tobacco (inhaled carcinogens):	
cigarettes>cigars	**85–87%**
Second-hand passive smoke	**5–7%**
Other(s)	**5–7%**
Radon	
Asbestos (co-factor)	
Uranium	
Therapeutic RT	
Marijuana	
Beryllium	
Air pollutants (diesel, pitch, tar, arsenic, nickel, chronium, cadmium)	
Scar/Fibrosis	**1–2%**

RT=radiation therapy.

02 Lung Cancer Histology

	Total Incidence (%)
NSCLC	
Adenocarcinoma	**40–50**
Incidence rising (especially in women); peripheral locational increased metastatic risk; less tightly linked to cigarettes versus other cell types.	
Squamous	**20–30**
Incidence declining; central location; decreased metastatic risk; tighter smoking linkage	
Large	**5–10**
Usually peripheral; may be extremely aggressive	
SCLC	**15–20**
APUD cells; central presentation, highly aggressive; presumed metastatic at dx; tightest smoking link	
Carcinoid	**1–3**
Morphologically similar to SCLC; "blander" histo appearance; usually localizaed +/- endobronchial; decreased metastatic risk.	

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; APUD=amine percursor uptake and decarboxylation.

03 Lung Cancer Presentation

- **Asymptomatic** (accidental pick-up)
- **Local** (cough, dyspnea, hoarseness, wheezing, pleurisy, chest pain)
- **Systemic** (bone, brain, liver)
- **Paraneoplastic** (tumoral hormonal)
  - Decreased sodium (NSAID)
  - Increased calcium (increased PTH)
  - HPOA
  - Cachexia

NSAID=non-steroidal anti-inflammatory drug; PTH=parathyroid hormone; HPOA=hypertrophic pulmonary osteoarthropathy.

04 Lung Cancer Diagnosis

Sputum Cytology: non-invasive; low-tech

Bronchoscopy: assess airway.
Indication: all central tumors; surgical candidate

Transthoracic FNA: CXR or CT guided
Indication: peripheral lesions; 15% F(-)

Mediastinoscopy: assess mediastinal nodes
Indication: surgical candidates

Vats: less invasive than thoracotomy
Indication: small, visible, peripheral lesions

Node Biopsy: supraclavicular, cervical nodes

FNA=fine-needle aspiration; CXR=chest x-ray; CT=computed tomography; F(-)=false negative.

05 Basic Lung Cancer Work-Up

- **CXR and CT scan** (chest, liver, adrenal)
- **Brain scan** (MRI, CT) – most
- **Bone scan** (most)
- **PET scan**

CXR=chest x-ray; CT= computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography.

06 NSCLC Prognostic Determinants

- **Stage** (Extent of disease)
- **Performance status**
- **Weight loss**
- **Gender**

NSCLC=non-small cell lung cancer.

07 ECOG/Zubrod Performance Status

0. Asymptomatic
Minimal symptoms; fully functional; maintaining ADL

1. Symptomatic
Able to carry out all ordinary tasks

2. Symptomatic
Compromised; 50% waking hours in bed

3. Symptomatic
Severly compromised; 50% waking hours in bed

4. Symptomatic
Bedridden; often moribund

ECOG=Eastern Cooperative Oncology Group; ADL=activites of daily living.

08 NSCLC Surgery

- **Cornerstone of treatment**
- **Anatomic resection:** important
- **Node sampling/dissetion:** crucial
- **Potential role:** isolated metastases

NSCLC=non-small cell lung cancer.

09 NSCLC Radiation Therapy

Surgically unresectable/medically inoperable (minimal dose 60 Gy)

Other curative venues:
- Adjuvant treatment after surgery (N1, N2): 50–55 Gy
- Pre-op in locally advanced stage III/Pancoast: 45–54 Gy

Palliative Role
- Local (SVC syndrome, hemoptysis; post-obstructive pneumonia)
- Brain
- Bone
- Spinal cord

Research arena
- 3-D conformal (IMRT)
- Acceleration
- Hyperfractionated
- Limiting toxicity (mcoprotectants)

NSCLC=non-small cell lung cancer; N=node; SVC=superior vena cava; IMRT=intensity modulated radiotherapy.

10 NSCLC: Standard Agents

Old (pre-1990)
Cisplatin
Etoposide
Vinblastine
Ifosfamide
Mitomycin-C

New (post-1990)
Paclitaxel
Docetaxel
Gemcitabine
Vinorelbine
Irinotecan

Investigatinal
MTA
Oxaliplatin
UFT

NSCLC=non-small cell lung cancer; MTA=multitargeted antifal; UFT=uracil/ftorafur.

11 NCCN Chemotherapy Guidelines for NSCLC

- Chemotherapy is indicated in PS 0–2 patients with advanced or recurrent NSCLC, and in combined modality therapy in locally advanced NSCLC.
- In locally advanced NSCLC, six separate studies have demonstrated the superiority of chemoradiation over radiation alone: three in the induction setting; three testing the concept of radiosensitization; in addition two studies showed superiority of concurrent chemoradiation to sequentia chemoradiation. Two separate studies have also confirmed a benefit for induction chemotherapy followed by surgery, compared to surgery alone in resectable locally advanced NSCLC.
- Cisplatin-based combination have proven superior to best supportive care in advance, incurable disease, with improved QOL, better symptom control, 6–12 week improvement in median survival and a doubling of 1-year survival rates (absolute 10% to 15% improvement).
- Cisplatin or carboplatin have proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, and tirapazamine.
- Vinorelbine, gemcitabine, or tirapazamine in combination with cisplatin has proven superior to cisplatin alone; and vinorelbine, irinotecan, or paclitaxel in combination with cisplatin, has proven superior to older agent cisplatin combinations.
- New agent/non-platinum combinations are reasonable alternatives if available phase I/II data show activity and tolerable toxicity.
- Single agent therapy is a reasonable alternative in PS 2 patients.
- Systemic chemotherapy is not indicatied in PS 3 or PS 4 patients.

NCCN=National Comprehensive Cancer Network; PS=performance status; QOL=quality of life.

12 SCLC

- **Chemotherapy:** cornerstone of treatment
- **Limited disease:** concurrent chemoradiation is the best hope of long-term survival
- **Extensive disease:** chemotherapy +/- radiation
- **Surgery:** limited role, reserved for very early stage SCLC (confined to chest without nodal invasion)
- **PCI:** eradication of occult, microscopic brain metastases before they grow clinically evident

SCLC=small cell lung cancer; PCI=prophylactic cranial irradiation.

13 SCLC: Standard Regimens (2000)

- Etoposide+Cisplatin
- Etoposide+Carboplation
- Irinotecan+Cisplatin
- CAV
- Topotecan
- Paclitaxel

SCLC=small cell lung cancer; CAV=cyclophosphamide, adriamycin, vincristine.

14 Anatomical Staging for Lung Cancer

DEFINITIONS

Primary Tumor (T)

Tx	Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of tumor
Tis	Carcinoma *in situ*
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in main bronchus)
T2	Tumor with any of the following features of size or extent: - More than 3 cm in greatest dimension. - Involves main bronchus, 2 cm or more distal to the carina. - Invades the visceral pleura. - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumor), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; separate tumor nodule(s) in the same lobe; or tumor with a malignant pleural effusion

***The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.**

****Most pleural effusions associated with lung cancer are due to tumor. There are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is nonbloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.**

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No lymph nodes metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the tumor
N2	Metastasis to ipsilateral mediastinal and/or sub carinal lymph node
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
MX	Distant metastasis cannot be assessed
MO	No distant metastasis
M1	Distant metastasis present (includes synchronous separate nodule(s) in a different lobe)

Stage Grouping

Occult	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

AJCC=American Joint Committee on Cancer; T=tumor; N=node; M=metastasis.

15 CALGB: Randomized Phase II Study in NSCLC

CALGB: Randomized Phase II Combined Modality Study In Unresectable, Regionally Advanced NSCLC[2]

Schema	**CYCLE NUMBER**			
Cycle (day)	1 (1)	2 (22)	3 (43)	4 (64)
Cisplatin	X	X	X	X
Experimental Rx	X	X	X	X
TRT	43–47	50–54	57–61	64–68 71–75 78–82
Doses				
Cisplatin (mg/m^2)	80	80	80	80
Gemcitabine (mg/m^2 days 1 and 8)	1,250	1,250	600	600
Vinorelbine (mg/m^2 days 1 and 8)	25	25	15	15
Paclitaxel (mg/m^2/3^o day 1)	225	225	135	135

Randomized Phase II Trial of Cisplatin-New Agent Doublets in Locally Advanced NSCLC[2]

% Toxicities Gr 3(4)

ARM	***GC***	***PC***	***VC***
N	63	60	58
Induction Chemotherapy			
ANC	46	52	52
Plts	23	0	2
Concurrent Chemotherapy/RT			
ANC	49 (13)	48 (24)	27 (6)
Platelets	55 (25)	6 (0)	0 (0)
Esophageal	56 (14)	35 (4)	24 (11)
Pulmonary	11	16	15

Randomized Phase II Trial of Cisplatin-New Agent Doublets in Locally Advanced NSCLC Outcome

ARM	**G**	**P**	**V**
N	63	60	58
OR Induction % (CR/PR)	0/32	0/27	2/34
OR% (CR/PR)	2/61	12/38	10/47
FFP median (months)	8	8	12
LF (%)	29	17	31
LF/DR (%)	12	22	19
DR (%)	22	28	22
Median survival (months)	17.2	14.1	17.7
1-year OS (%)	63	63	67

CALGB=Cancer and Leukemia Group B; TRT=thoracic radiotherapy; G=gemcitabine; P=paclitaxel; V=vinorelbine; ANC=absolute neutrophil count; RT=radiation therapy; CR/PR=complete remission/partial remission; OR=overall response; FFP=freedom from progression; LF/DR=local failure/distant recurrence; DR=distant recurrence; OS=overall survival.

16 Comparison of SWOG 9504 and 9019

Study	Arm	N	MS (months)	Survival Rates 1-year (%)	2-year (%)	3-year (%)
S9504	PE/RT→D	83	22	78	50	40
S9019	PE/RT→PE	50	15	58	34	16

N=node; MS=median survival; PE/RT→D=cisplatin etoposide/radiation therapy→docetaxel.

17 CPT-11/cDDP (IP) Versus VP-16/cDDP (EP) EXT SCLC: JCOG PHASE III[3]

- Targeted 230 patients; accrual stopped after 154 because of statistically significant difference in survival.
- Arms well balanced with respect to pre-Tx traits

ARM	IP	EP
N	77	77
Irinotecan (mg/m^2)	60 (days 1, 8, and 15)	–
Cisplatin (mg/m^2)	60 (day 1)	80 (day 1)
Etoposide (mg/m^2)	–	100 (days 1–3)
Cycle Length (weeks)	4	3

CPT-11=CPT-11 irinotecan; cDDP=cisplatin; IP=irinotecan/cisplatin; VP-16=setopside; EP=etoposide/cisplatin; EXT SCLC=extensive small cell lung cancer; JCOG=Japan Clinical Oncology Group; N=number of patients.

18 CPT-11 (IP) Versus VP-16/cDDP (EP) in EXT SCLC: JCOG PHASE III[3]

	IP	EP	*p*-value
Gr 3 WBC ↓ (%)	27	52	.003
Gr 3 ANC ↓ (%)	66	92	.0002
Gr 3 Plt ↓ (%)	5	19	.01
Gr 3 Diarrhea (%)	16	0	.0001
Tx Deaths (%)	3 (4)	1	NSS

CPT-11=CPT=11 irinotecan; IP=irinotecn/cisplatin, VP-16=etopside; cDDP=cisplatin; EXT-SCLC=extensive small cell lung cancer; JCOG=Japan Clinical Oncology Group; WBC=whole blood count; ANC=absolute neutrophil count; Plt=platelets; NSS=not statistically significant.

19 EP→T Versus EP

Median age: 63; PS 2 (15%)

Category	Entrants	OBS	T	*p*-Value
Eligible	405	112	115	N/A
OR (CR)%	35 (3)	(-)	7 (2)	N/A
MS (months)	9.5	8.9*	9.3*	.71
PFS (months)	N/A	2.3	3.6	.0001
1-year OS (%)	35	27	25	N/A
Gr 4 ANC ↓ (%)	50	0	60	N/A
Gr 3–5 Infection(%)	8	0	4.5	N/A
Gr 4 Plt ↓ (%)	3	0	13	N/A
Gr 3 H/H ↓ (%)	9.5	0	21(3)	N/A
Any Gr 3(4) (%)	75 (50)	N/A	91(61)	N/A

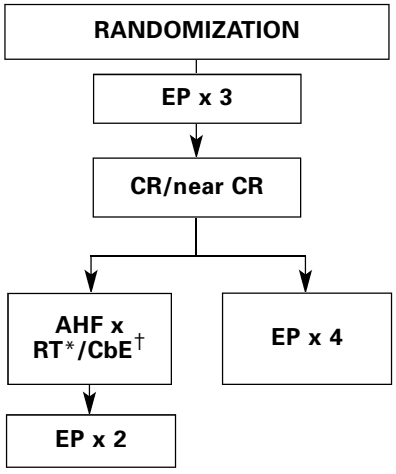
***from step 2 (after EP X 4)**

CONCLUSION:

Topotecan consolidation after PE does not enhance outcome.

EP=etoposide+cisplatin; T=tumor; PS=performance status; OBS=observation; N/A=not applicable; OR=overall response; MS=median survival; PFS=progression free survival; OS=overall survival; ANC=absolute neutrophil count; .

20 ED-SCLC: ROLE of RT 4



***AHF x RT: 54 Gy/36 fx**

† Weekly CbE

ED-SCLC=extensive disease small cell lung cancer; EP=etoposide+cisplatin; CR=complete remission; AHF=accelerated hyperfractional radiotherapy; RT=radiation therapy; CbE=carboplatin+etoposide.

21 ED-SCLC: ROLE of RT[4]

	Median Survival (months)	5-Year OS (%)
Standard	11	3.7
ACC HF x RT*	17	9.1 (p=.041)

*^RT-assocoated esophagitis

Trend: ^ local control (p=.062)

ED-SCLC=extensive disease small cell lung cancer; XRT=radiation therapy; OS=overall survival; ACC=accelerated.

22 PET and RT in Limited SCLC: Agents

Agents	RTOG[5] Dose (mg/m²)	ECOG[6] Dose (mg/m²)
Etoposide	80 IV day 1; 160 PO days 2 and 3	80 days 1–3 cycles 1 and 2 (60 days 1–3 cycles 3 and 4)
Cisplatin	60 day 1	80 day 1
Paclitaxel	135 day 1 (175 day 1 cycles 2–4)	170 day 1 cycles 1 and 2; (135 days 1 cycles 3 and 4)
RT	1.5 Gy/fx BID x 5 days/week x 3	1.8 Gy/fx x 35 fx
Chemo-RT	Cycle 1 (day 1)	Cycle 3 (day 43)
Accrual (dates)	55 (11/96–3/98)	63 (12/97–10/98)
Median age (years)	*56*	*62*
5% weight loss (lbs)	*26*	*26*

PET=cisplatin etoposide paclitaxel; RT=radiation therapy; LTD=limited; RTOG=Radiation Therapy Oncology Group; ECOG=Eastern Cooperative Oncology Group; IV=intravenous.

23 PET and RT in Limited SCLC: Toxicities

	RTOG (Ettinger)[5] Dose (mg/m²)	ECOG (Sandler)[6] Dose (mg/m²)
Toxicities: % Gr 3(4)		
N/V	19 (4)	8 (1)
ANC	75 (43)	76 (59) NF-16%
Plt	8 (4)	8 (7)
Esoph	36 (4)	28 (8)
Lung	9 (0)	3 (0)
OR (CR)	96 (16)	64 (13)
TTP	1 year	8.6 months
Median survival	24 months	16.8 months
PFS (median)	12 months	8.6 months
1-year OS	83%	63%
2-year OS	50%	N/A

PET=positron emission tomography; RT=radiation therapy; SCLC=small cell lung cancer; RTOG=Radiation Therapy Oncology Group; ECOG=Eastern Cooperative Oncology; N/V=no value; NF=neutropenic faver; ANC=absolut neutrophil count; OR=overall response; CR=complete remission; TTP=time to progression; PFS=progression free survival; OS=overall survival; N/A=not available.

24 Salvage Tx: Topotecan Versus CAV

	T	CAV	*p*-Value
N	107	104	NSS
OR (%)	24.3	18.3	NSS
TTP (weeks)	13.3	12.3	.552
Median survival (weeks)	25	24.2	.795

T=topotecan; CAV=cyclophosphamide-adriamcin-vincristine; N=number of patients; NSS=not statistically significant; OR=overall response; TTP=time to progression.

Common Chemotherapy Regimens : NSCLC

25 Etoposide + Cisplatin[7-11]

Indications

- Advanced NSCLC
- Induction treatment before resection or local RT
- Concurrent chemoradiation in locally advanced NSCLC

Outcomes

- Standard treatment through 1980s and early 1990s
- Inferior to cisplatin-paclitaxel in ECOG trial 5572
- Lower response rate, but equivalent survival versus carboplatin-paclitaxel and gemcitabine-cisplatin in trials sponsored by pharmaceutical companies

Instructions/Precautions

- Consider in patient
- Hyperhydrate patient with saline solution and mannitol for rapid diuresis
- Repeat chemotherapy usually at 3-week intervals when WBC >3 x 10^9/L, platelet count >100 x10^9/L
- Assess neurologic status periodically
- Monitor renal function on a daily basis
- Postpone therapy WBC <3 x 10^9/L and/or ANC <1,500/µL, platelet count <100 x 10^9/L
- Etoposide must be infused slowly, over at least 30 minutes, preferably 1 hour
- Check infusion site for signs of phlebitis
- Monitor BP every 15 minutes during first hour of therapy
- Highly emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Common: Alopecia, anemia, emesis, myelosuppression, nausea

Rare: Anaphlaxis, diarrhea, hypersensitivity, nephrotoxicity (if properly hydrated), peripheral neuropathy (can also be cumulative)

Very Rare: Carcinogenesis

Others: Ototoxicity, phlebitis

Regimen

Etoposide: 100–120 mg/m^2 QD x 3
Cisplatin: 60–75 mg/m^2 IV day 1 (or 20–30 mg/m^2 IV every day x 3) ***or***
Etoposide: 50 mg/m^2 QD x 5 days 1–5, days 29–33 (during RT)
Cisplatin: 50 mg/m^2 days 1 and 8, days 29 and 30 (during RT)

NSCLC=non-small cell lung cancer; RT = radiation therapy; ECOG=Eastern Cooperative Oncology Group; WBC=whole blood count; ANC=absolute neutrophil count; BP=blood pressure; IV=intravenous.

26 Gemcitabine[7,9,10,12-17]

Indications

- Advanced stage IIIB/IV NSCLC

Outcomes

- Reproducible 20% response rate
- Well-tolerated in elderly and PS 2 patients
- Equivalent response rates, TTP, and survival versus etoposide-cisplatin

Instructions/Precautions

- Outpatient
- Monitor CBC and platelet count weekly
- Monitor liver function before commencing therapy and every month during treatment
- Monitor baseline weight and measure during therapy. Treat weight gain and edema with diuretics
- Treat skin reactions with topical corticosteroids or, if necessary, oral corticosteroids
- Discontinue therapy if patient develops severe skin reactions
- Infuse gemcitabine slowly over 30 minutes (minimum)
- Mildly moderately emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Common: Myelosuppression (especially platelets)

Rare: Dyspnea, hematuria, maculopapular rash

Others: Flu-like syndrome, proteinuria, pruritis

Regimen

Gemcitabine: 1,000 mg/m^2 IV days 1 and 8 every 3 week on days 1, 8, and 15 every 4 weeks.

NSCLC=non-small cell lung cancer; PS=performance status; TTP=time to progression; CBC=complete blood count.

27 Gemcitabine + Cisplatin[7,9,10,18-25]

Indications

- Advanced NSCLC: recurrent; stage IV and/or IIIB

Outcomes

- Superior response and survival versus single agent cisplatin
- Superior response rate versus MIC and EP
- Cumulative thrombocytopenia can lead to day 15 dose omissions/reductions

Instructions/Precautions

- Inpatient day cisplatin given; outpatient for subsequent gemcitabine doses.
- Hyperhydrate with saline solution and mannitol for rapid diuresis.
- Repeat chemotherapy when WBC >3 x 10^9/L (ANC >1,500), platelet count >100 x 10^9/L.
- Assess neurologic status periodically.
- Monitor renal function on a weekly basis.
- Monitor CBC and platelet count weekly.
- Monitor liver function before commencing therapy and every month during treatment.
- Monitor baseline weight and measure during therapy. Treat weight gain and edema with diuretics.
- Treat skin reactions with topical corticosteroids.
- Discontinue if patient develops severe skin reactions.
- Infuse gemcitabine slowly over 30 minutes.
- Highly emetogenic (see essay: antiemetic therapy).

Adverse Reactions

Very Common: Anemia, emesis, myelosuppression

Occasional: Nephrotoxicity, ototoxicity,peripheral neuropathy

Rare: Anaphylaxis, dyspnea, flu-like syndrome, maculopapular rash, pruritis

Others: Diarrhea, hematuria, proteinuria

Regimen

Standard:

Gemcitabine: 1 g/m^2 days 1, 8 +/- 15
Cisplatin: 100 mg/m^2 day 1 (or days 2 or 15)
Cycle Length: 21–28 days

Alternative (Preferred):

Gemcitabine: 1 g/m^2 days 1 and 8
Cisplatin: 70 mg/m^2 day 1
Cycle Length: 21 days

NSCLC=non-small cell lung cancer; MIC=mitomycin, ifosfamide, cisplatin; EP=etoposide, cisplatin; WBC=whole blood count; ANC=absolut neutrophil count.

28 MIC[7,28]

Indications

- Stage IIIA, IIIB, or IV
- Induction therapy before surgical resection for definitive local RT

Outcomes

- Induction treatment before surgery in locally advanced resectable NSCLC superior to surgery alone
- Superior to best supportive care in a United Kingdom trial in advanced disease patients yielding improved QOL; and in combination with RT superior to RT alone in stage III NSCLC.

Instructions/Precautions

- In patient (can also be given as outpatient)
- Hyperhydrate: saline solution and mannitol for rapid diuresis
- Repeat chemotherapy when WBC >3 x 10^9/L (ANC >1,500/mL), platelet count >100 x 10^9/L
- Assess neurologic status periodically
- Monitor renal function every week
- Monitor CBC and platelet count weekly
- Monitor liver function and pulmonary function periodically
- Postpone if WBC 3 x 10^9/L QHS platelet count 100 x 10^9/L
- Check infusion site for signs of phlebitis
- Monitor BP every 15 minutes during first hour of therapy
- Monitor for fluid retention
- Highly emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Common: Anemia, emesis, myelosuppression,nausea

Rare: Anaphylaxis, pneumonitis, peripheral neuropathy (cumulative)

Very Rare: Carcinogenesis

Others: Alopecia, bladder toxicity (prevented by MESNA), diarrhea, fluid retention, hypersensitivity, liver enzymes elevated, nephrotoxicity, ototoxicity, phlebitis

Regimen

Mitomycin: 6 mg/m^2 day 1 (1 VB)

Ifosfamide: 3 g/m^2/day 1

MESNA: 1 gm/m^2/3°

Cisplatin: 50 mg/m^2/1 hour

Cycle: 3 week intervals

MIC=mitomycin+ifosfamide+cisplatin; RT=radiation therapy; NSCLC=non-small cell lung cancer; QOL=quality of life; WBC=whole blood count; ANC=absolute neutrophil count; CBC=complete blood count; BP=blood pressure.

29 Irinotecan[7,9,10,29-31]

Indications

- Single agent therapy in advanced NSCLC

Outcomes

- Response rate 10% to 30%
- Equivalent outcome to cisplatin-vindesine in Japanese studies

Instructions/Precautions

- Outpatient
- Monitor CBC and platelet count weekly
- Monitor for elevated temperature
- Administer antidiarrheal medication as needed (immediate intervention at first sign of diarrhea); recommend: Loperamide 4 g at onset, then 2 mg every 2° prn
- Emetogenicity (moderate)
- Monitor for cholinergic symptoms; use subcutaneous atropine if symptoms occur

Adverse Reactions

Common: Diarrhea (can be life-threatening if not treated quickly)

Rare: Dyspnea, hematuria

Others: Abdominal cramps, fever, liver enzymes elevated, myelosuppression

Regimen

Irinotecan: 125 mg/m^2 every week x 4 every 6 weeks

Irinotecan: 125 mg/m^2 days 1 and 8 every 3 weeks

Irinotecan: 300 mg/m^2 IV every 3 weeks QHS G-CSF

NSCLC=non-small cell lung cancer; CBC=complete blood count; G-CSF=granuloctye colony-stimulating factor.

30 Vinorelbine[7,9,10,32-34]

Indications

- Stage IIIB/IV NSCLC: single agent or in combination with cisplatin
- Elderly (>70 years of age) NSCLC patients

Outcomes

- Superior response rate and survival versus 5-FU/LV
- Superior survival rate and improved QOL versus best supportive care in elderly patients (>70 years of age)

Instructions/Precautions

- Outpatient setting
- Consider lowering dose in patients with impaired hepatic function or advanced age
- Postpone therapy or lower dose of vinorelbine if WBC <3 x 10^9/L (ANC 1,500/μL), platelet count <100 x 10^9/L
- Low WBC may be treated with colony stimulating factors
- Extravasation of vinorelbine will cause tissue necrosis; use central access device, if possible
- Monitor carefully for signs of neurotoxicity
- Give metoclopramide 10–20 mg before and 4 hours after dosing with vinorelbine to treat constipation and emesis
- Moderately emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Common: Myelosupression

Mild: Alopecia

Others: Constipation, emesis, neurotoxicity

Regimen

Vinorelbine: 25–30 mg/m^2 every week or (days 1 and 8 every 3 weeks or days 1, 8, and 15 every 4 weeks)

NSCLC=non-small cell lung cancer; QOL=quality of life; 5-FU/LV=5-fluorouracil/leucovorin; WBC=whole blood count; ANC=absolut neutrophil count.

31 Vinorelbine + Cisplatin[7,9,10,35,36]

Indications

- Advanced stage IV or IIIB or recurrent NSCLC

Outcomes

- Superior to single agent cisplatin in SWOG study
- Superior to single agent vinorelbine and combination cisplatin-vindesine in French trials
- Equivalent to carboplatin-paclitaxel in advanced NSCLC (SWOG) with an OR of 25%, TTP of 4 months, median survival of 8 months, and 1-year OS of 35%

Instructions/Precautions

- cDDP: inpatient; subsequent vinorelbine: outpatient
- Consider lowering dose in patients with impaired hepatic function
- Postpone therapy or lower dose of vinorelbine if WBC <3 x 10^9/L (ANC <1,500/μL), platelet count <100 x 10^9/L
- Low WBC may be treated with colony stimulating factors
- Extravasation of vinorelbine will cause tissue necrosis
- Hyperhydrate with saline solution and mannitol for rapid diuresis
- Repeat chemotherapy when WBC >3 x 10^9/L, platelet count >100 x 10^9/L
- Assess neurologic status periodically
- Monitor renal function every week
- Monitor carefully for signs of neurotoxicity
- Give metoclopramide 10–20 mg before and 4 hours after dosing with vinorelbine to treat constipation and emesis
- Highly emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Common: Anemia, emesis, myelosuppression, nausea

Occasional: Neurotoxicity

Rare: Nephrotoxicity

Others: Alopecia, anaphylaxis, constipation, diarrhea, ototoxicity, peripheral neuropathy

Regimen

Cisplatin: 100 mg/m^2 IV every 4 weeks

Vinorelbine: 25 mg/m^2 IV every week

NSCLC=non-small cell lung cancer; SWOG=Southwestern Oncology Group; OR=overall response; TTP=time to progression; OS=overall survival; cDDP=cisplatin; WBC=whole blood count; ANC=absolut neutrophil count; IV=intravenous.

32 Paclitaxel[7,9,10,37-47]

Indications

- Advanced NSCLC (recurrent; stage IV, IIIB)
- Locally advanced NSCLC: concurrent with RT

Outcomes

- Superior to best supportive care in advanced NSCLC
- Single agent response rates 20% to 30%
- Weekly treatment at doses of 80–100 mg/m^2 (well tolerated in elderly and/or PS 2)

Instructions/Precautions

- Outpatient
- Prepare for anaphylactic reaction
- Premedicate with H1 blocker, diphenhydramine (50 mg IV) and an H2 blocker, such as cimetidine or ranitidine, 30 minutes before dose
- Premedicate with dexamethasone 20 mg IV 30 minutes before dose
- Paclitaxel must be administered in glass, polyolefin, or polypropylene containers using polyethylene-lined tubing and a 0.22-µm filter
- Acute cardiac arrhythmias may develop during infusion, resulting in bradycardia and hypotension
- Monitor CBC weekly, including differential and platelet count
- Administer antiemetics appropriate for mildly moderately emetogenic chemotherapy (see essay about antiemetic therapy)
- Repeat chemotherapy when WBC >3 x 10^9/L and platelet count >100 x 10^9/L

Adverse Reactions

Common: Alopecia, arthralgia/myalgia, hypersensitivity and anaphylaxis (common with prophylaxis), peripheral neuropathy (also cumulative)

Mild: Myelosuppression

Rare: Emesis

Others: Cardiac arrhythmia

Regimen

Standard: 200–225 mg/m^2 every 3 weeks

Weekly: 80–100 mg/m^2 weekly or every week x 3 every 4 weeks

Weekly: 150 mg/m^2 x 6 every 8 weeks

NSCLC=non-small cell lung cancer; PS=performance status; IV=intravenous; CBC=complete blood count; WBC=whole blood count.

33 Docetaxel[7,9,10,48-50]

Indications

- Advanced chemotherapy-naïve NSCLC: recurrent; stage IV, IIIB
- Salvage treatment in platinum exposed patients

Outcomes

- Single agent response rates: 20% to 30%
- Superior survival and quality of life versus best supportive care in salvage treatment after prior cDDP
- Superior survival and QOL versus vinorelbine or ifosfamide after prior cDDP

Instructions/Precautions

- Outpatient
- Premedicate with 8 mg dexamethasone PO BID, beginning the day before therapy and continuing for 3–5 days total; may attenuate prophylaxis to 8 mg previous evening; prior to infusion and 8 hours later
- Dilute taxotere in 0.9% saline or D5W solution
- Monitor CBC weekly
- Monitor fluid input and output and weight gain weekly
- Mildly emetogenic

Adverse Reactions

Common: Fluid retention syndrome (if not given steroids), neutropenia

Mild: Nausea/emesis, peripheral neurotoxicity

Rare: Thrombocytopenia

Others: Alopecia, anaphylaxis, malaise

Regimen

Taxotere: 75–100 mg/m^2 IV over 1-hour infusion, every 3 weeks

Taxotere: 50 mg/m^2 IV over 1-hour infusion on days 1 and 8 (3-week cycle) **or**

Taxotere: 30–35 mg/m^2 every week, three out of four weeks, or four out of six weeks

NSCLC=non-small cell lung cancer; cDDP=cisplatin; QOL=quality of life; D5W=dextrose in H_2O; CBC=complete blood count; IV=intravenous

34 Docetaxel + Cisplatin[7,9,10,51,52]

Indications

- Advanced NSCLC: recurrent; stage IIIB/IV

Outcomes

- Superior to vinorelbine-cisplatin

Instructions/Precautions

- Inpatient
- Prepare for anaphylactic reaction
- Premedicate with H1 blocker, diphenhydramine, and an H2 blocker such as cimetidine or ranitidine 30 minutes before dose
- Premedicate with 8 mg dexamethasone PO BID; beginning day before therapy, continuing for 3–5 days
- Paclitaxel must be administered in glass, polyolefin, or polypropylene containers, using polyethylene-lined tubing and a 0.22-μm filter.
- Acute cardiac arrhythmias may develop during infusion, resulting in bradycardia and hypotension.
- Hyperhydrate with saline solution and mannitol for rapid diuresis.
- Assess neurologic status periodically.
- Monitor renal function on weekly basis.
- Monitor CBC weekly, including differential and platelet count.
- Administer antiemetics appropriate for highly emetogenic chemotherapy (see essay about antiemetic therapy).
- Repeat chemotherapy when WBC >3 x 10^9/L and platelet count >100 x 10^9/L.

Adverse Reactions

Expected: Alopecia

Common: Fluid retention syndrome (if not given steroids), myelosuppression (can be severe), nausea/emesis, neurotoxicity

Rare: Cardiac arrhythmia, nephrotoxicity, ototoxicity

Cumulative: Peripheral neuropathy

Others: Hypersensitivity and anaphylaxis, malaise

Regimen

Docetaxel: 75 mg/m^2/1° every 3 weeks

Cisplatin: 75 mg/m^2/1° every 3 weeks

NSCLC=non-small cell lung cancer; CBC=complete blood count; WBC=whole blood count.

35 Paclitaxel + Cisplatin[7,9,10,53-55]

Indications

- Advanced NSCLC: recurrent; stage IIIB/IV

Outcomes

- Superior to etoposide-cisplatin (ECOG 5592)

Instructions/Precautions

- Inpatient
- Prepare for anaphylactic reaction
- Premedicate with H1 blocker, diphenhydramine, and an H2 blocker such as cimetidine or ranitidine 30 mins before dose
- Premedicate with dexamethasone 20 mg IV 30 minutes before dose
- Paclitaxel must be administered in glass, polyolefin, or polypropylene containers, using polyethylene-lined tubing and a 0.22-μm filter
- Acute cardiac arrhythmias may develop during infusion, resulting in bradycardia and hypotension.
- Hyperhydrate: saline solution and mannitol for rapid diuresis.
- Assess neurologic status periodically.
- Monitor renal function on weekly basis.
- Monitor CBC weekly, including differential and platelet count.
- Administer antiemetics appropriate for highly emetogenic chemotherapy (see essay about antiemetic therapy).
- Repeat chemotherapy when WBC >3 x10^9/L and platelet count >100 x 10^9/L.

Adverse Reactions

Common: Nausea/emesis, neurotoxicity

Expected: Alopecia

Moderate: Arthralgia/myalgia

Rare: Cardiac arrhythmia, nephrotoxicity, ototoxicity

Cumulative: Peripheral neuropathy

Others: Hypersensitivity and anaphylaxis, myelosuppression

Regimen

Standard (ECOG 5592):

Paclitaxel: 135 mg/m^2/24 hours ↓ 3 weeks

Cisplatin: 75 mg/m^2/1° ↓ 3 weeks

Alternative:

Paclitaxel: 175 mg/m^2/3 hour ↓ 3 weeks

Cisplatin: 80 mg/m^2/1 hour ↓ 3 weeks

NSCLC=non-small cell lung cancer; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; CBC=complete blood count; WBC=whole blood count.

36 Paclitaxel + Carboplatin[7,9,10,56-64]

Indications

- Advanced NSCLC: recurrent; stage IIIB/IV
- Locally advanced NSCLC: induction before RT and/or concurrent with RT

Outcomes

- Equivalent to etoposide-cisplatin (ECOG 5592) vis-à-vis survival, TTP, with increased OR%, increased QOL
- Equivalent to vinorelbine-cisplatin vis-à-vis survival, TTP, and OR% in SWOG trial and Italian trial (Scagliotti)

Instructions/Precautions

- Outpatient
- Prepare for anaphylactic reaction
- Premedicate: H1 blocker, diphenhydramine, and H2 blocker such as cimetidine or ranitidine 30 minutes before dose
- Premedicate: dexamethasone 20 mg IV 30 minutes before dose
- Paclitaxel must be administered in glass, polyolefin, or polypropylene container susing polyethylene-lined tubing and a 0.22-µm filter
- Acute cardiac arrhythmias may develop during infusion, resulting in bradycardia and hypotension
- Assess neurologic status periodically
- Monitor CBC count weekly, including differential and platelet count
- Administer antiemetics appropriate for emetogenic chemotherapy (see essay about antiemetic therapy)
- Repeat chemotherapy when WBC >3 x 10^9/L and platelet count >100 x 10^9/L
- Monitor renal function every cycle (or weekly during RT)

Adverse Reactions

Expected: Alopecia

Common: Neurotoxicity

Moderate: Arthralgia/myalgia, nausea

Rare: Cardiac arrhythmia

During RT: Dermatitis, espophagitis, pneumonitis

Uncommon: Emesis

Others: Hypersensitivity,anaphylaxis,myelosuppression

Cumulative: Peripheral neuropathy

Regimen

Carboplatin: AUC 5–7.5
Paclitaxel: 200–225 mg/m^2/3 hours **or**
Carboplatin: AUC 2 Q week x 6–7 (during RT)
Paclitaxel: 45–50 mg/m2 Q week x 6-7 (during RT)

NSCLC=non-small cell lung cancer; RT=radiation therapy; ECOG=Eastern Cooperative Oncology Group; TTP=time to progression; OR=overall response; QOL=quailty of life; SWOG=Southwestern Onocology Group; IV=intravenous; CBC=complete blood count; WBC=whole blood count; AUC=area under time curve.

Common Chemotherapy Regimens : SCLC

37 Cyclophosphamide+Doxorubicin+Vincristine[7,9,10,66-68]

Indications

- Extensive SCLC

Outcomes

- Equivalent to etoposide-cisplatin in most extensive SCLC studies

Instructions/Precautions

- Outpatient
- Monitor cardiac function before treatment, including ECG and ejection fraction
- Discontinue therapy if patient develops cardiac failure. Risk of cardiomyopathy increases with total doxorubicin dose >450 mg/m^2
- Have anaphylaxis kit available during infusion of cyclophosphamide
- Ensure adequate oral fluid intake
- Advise patient to avoid caffeine-containing products
- Monitor CBC and platelet count weekly
- Monitor liver function every 3-4 weeks
- Postpone therapy if WBC <3 x 10^9/L, platelet count <100 x 10^9/L
- Extravasation of doxorubicin will cause tissue necrosis
- Lower doxorubicin dose if patient develops significant liver impairment
- Scalp cooling may reduce risk of alopecia
- Moderately emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Expected: Alopecia

Common: Myelosupression, nausea, emesis

Rare: Arrhythmia, bladder toxicity, cardiotoxicity (also cumulative)

Others: Carcinogenesis, liver enzymes elevated, mucositis, neurotoxicity, pneumonitis, vomiting

Regimen

Cyclophosphamide: 1,000 mg/m^2

Doxorubicin: 45–50 mg/m^2

Vincristine: 1.2 mg/m^2 (cap at 2 mg)

SCLS=small cell lung cancer; ECG=electrocardigram; CBC=complete blood count; WBC=whole blood count.

38 Etoposide + Cisplatin[7,9,10,68-70]

Indications

- Extensive SCLC
- Limited SCLC concurrent with standard RT (45 Gy)

Outcomes

- Equivalent to CAV in extensive disease
- Easier to integrate with RT in limited SCLC (compared with CAV)

Instructions/Precautions

- Inpatient
- Hyperhydrate with saline solution and mannitol for rapid diuresis
- Repeat chemotherapy usually at 3-week intervals when WBC >3 x 10^9/L, platelet count >100 x 10^9/L
- Assess neurologic status periodically
- Monitor renal function on a daily basis
- Postpone therapy if WBC <3 x 10^9/L and/or ANC <1,500/µL, platelet count <100 x 10^9/L
- Etoposide must be infused slowly, over at least 30 minutes and preferably 1 hour
- Check infusion site for signs of phlebitis
- Monitor blood pressure every 15 minutes during first hour of therapy
- Highly emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Common: Alopecia, anemia, emesis, myelosuppression, nausea

Rare: Anaphylaxis, diarrhea, hypersensitivity, nephrotoxicity (if properly hydrated), peripheral neuropathy (can be cumulative)

Very rare: Carcinogenesis

If given concurrently with RT: Dermatitis, esophagitis, pneumonitis

Others: Ototoxicity, phlebitis

Regimen

Etoposide: 100–120 mg/m^2 every day x 3

Cisplatin: 60–75 mg/m^2 IV day 1 (or 20–30 mg/m^2 IV every day x 3)

SCLC=small cell lung cancer; RT=radiation therapy; CAV=cyclophpsphamide adriamycin vincristine; WBC=whole blood count; ANC=absolut neutrophil count; IV=intravenous.

39 Carboplatin + Etoposide[7,9,10,71]

Indications

- Extensive SCLC
- Limited SCLC (compromised patients)

Outcomes

- Equivalent to etoposide-cisplatin in extensive SCLC studies with considerably less nonhematologic toxicity
- Suited for patients with compromised KPS, underlying hearing loss or sensory neuropathy, or baseline renal impairment.

Instructions/Precautions

- Outpatient
- Repeat chemotherapy at 3-week intervals once WBC has recovered to >3 x 10^9/L (ANC >1,500/μL)
- Postpone treatment if WBC <3 x 10^9/L, platelet count <100 x 10^9/L
- Monitor renal function each cycle
- Etoposide should be infused slowly, over >30 minutes and preferably 1 hour.
- Moderately emetogenic (see essay about antiemetic therapy)

Adverse Reactions

Common: Alopecia, anemia
Moderate: Emesis, nausea
Rare: Anaphylaxis, hypersensitivity, phlebitis
Extraordinarily Rare: Carcinogenesis
Others: Leukopenia, myelosuppression, thrombocytopenia

Regimen

Standard: Carboplatin: 300 mg/m^2/day
Etoposide: 100–125 mg/m^2/days 1, 2, and 3
Cycle: 3–4 week intervals
G-CSF in elderly patients or those with prior RT

Alternative: Carboplatin: AUC 5–6
Etoposide: 100–125 mg/m^2/days 1, 2, and 3
Cycle: 3–4 week intervals
G-CSF in elderly patients or those with prior RT

SCLC=small cell lung cancer; KPS=Kainotsky performance status; WBC=whole blood count; ANC=absolut neutrophil count.

40 Topotecan[7,9,10,72]

Indications

- Second-line treatment: chemosensitive relapse

Outcomes

- Equivalent to CAV vis-à-vis response rate, TTP, and survival in chemosensitive relapse (>60–90 days after prior treatment).
- Significant symptom benefit versus CAV

Instructions/Precautions

- Outpatient
- Repeat chemotherapy at 3 week intervals once WBC has recovered to >3 x 10^9/L (ANC >1500/μL); platelet >100,000/μL
- Postpone treatment if WBC <3 x 10^9/L, platelet count <100 x 10^9/L
- Monitor interim CBC closely
- Moderately emetogenic

Adverse Reactions

Common: Myelosuppression
Mild: Alopecia
Rare: Diarrhea, emesis, nausea
Severe: Anemia

Regimen

Topotecan: 1.5 mg/m^2 IV every day x 5 every 3 weeks*
Low threshold to add G-CSF or reduce duration of Tx to daily x 3–4 every 3 weeks

*A growing body of evidence has demonstrated that topotecan has activity at doses of less than the indicated 1.5 mg/m^2

CAV=cycolophosphamid-adriamycin-vincristine; TTP=time to progression; WBC=whole blood count; ANC=absolute neutophil count; CBC=complete blood count; G-CSF=granuloctye colony-stimulating factor.

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