LIPOSOMAL CISPLATIN

LIPOplatin

Dr. Saadettin KILIÇKAP
Hacettepe University Cancer Institute

Cisplatin

- A cytotoxic agent
- Effective in epitelial tumors
- Being used in treatment of many tumors as either single agent or in combined therapy

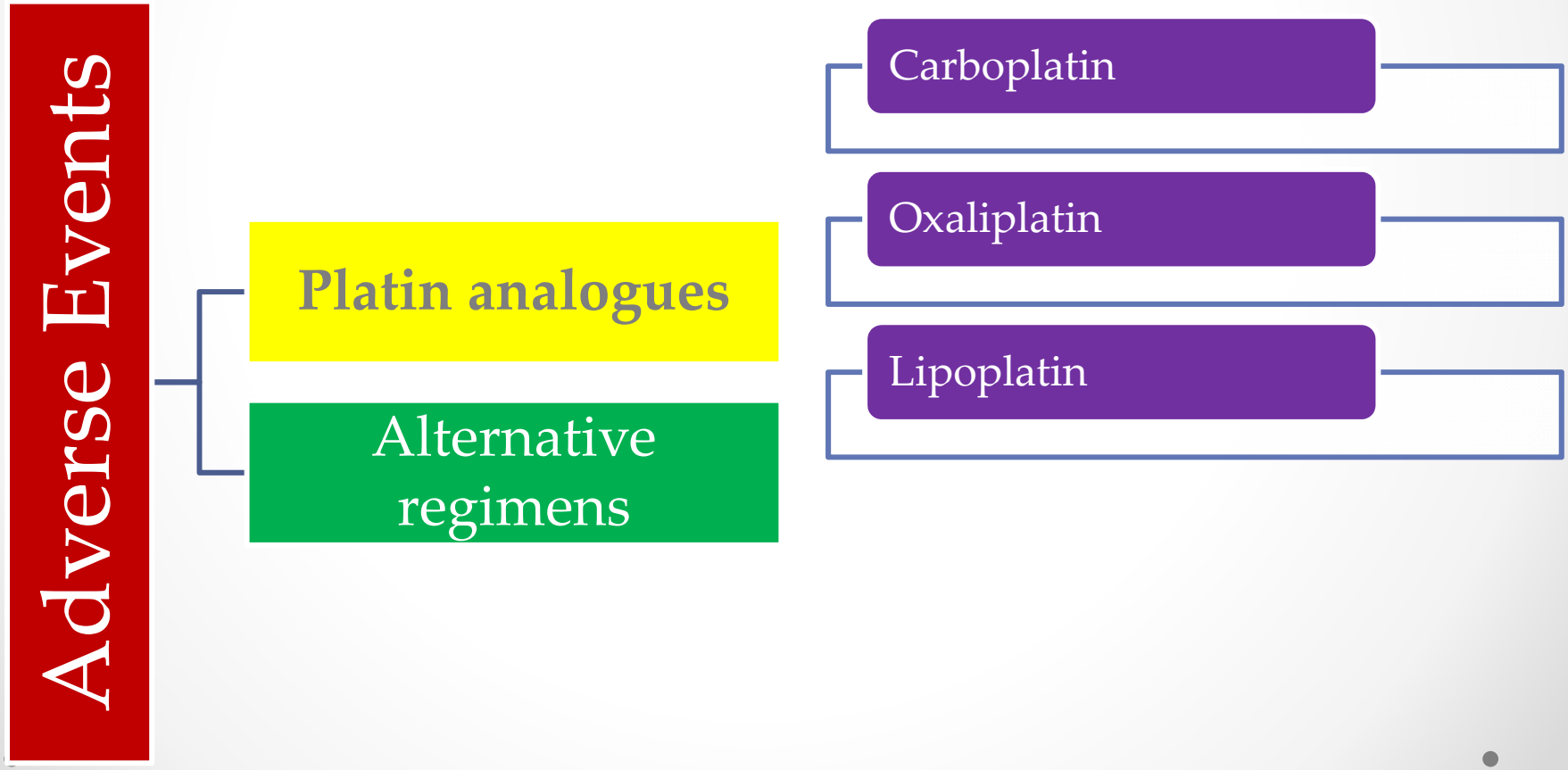
Cisplatin

Effective, but toxicity is a major concern

- Nausea-vomiting
- Nephrotoxicity
- Ototoxicity
- Neurotoxicity
- GIS toxicity
- …

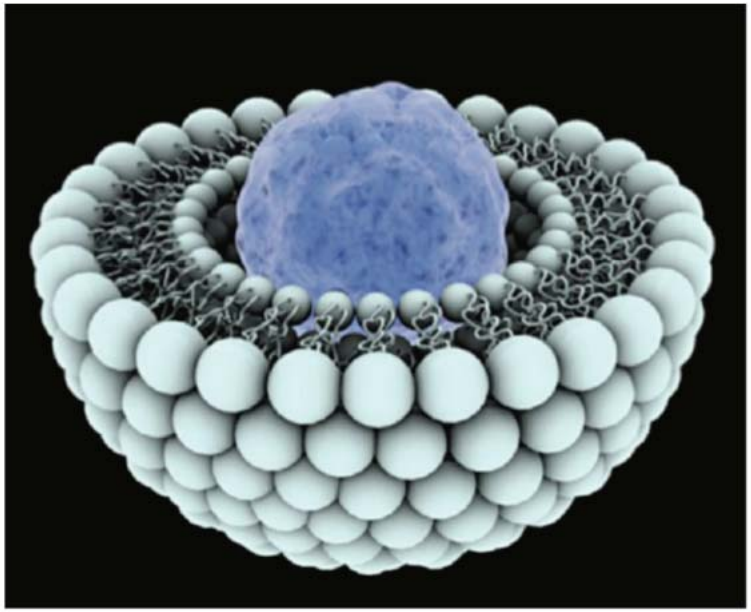
Cisplatin

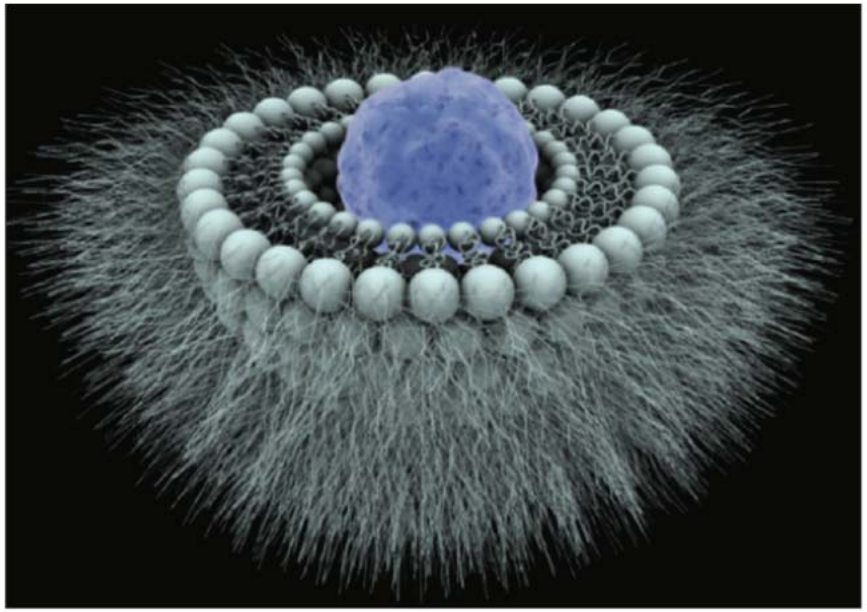
Adverse events resulted in need for optional treatments



LIPOSOMAL CISPLATIN

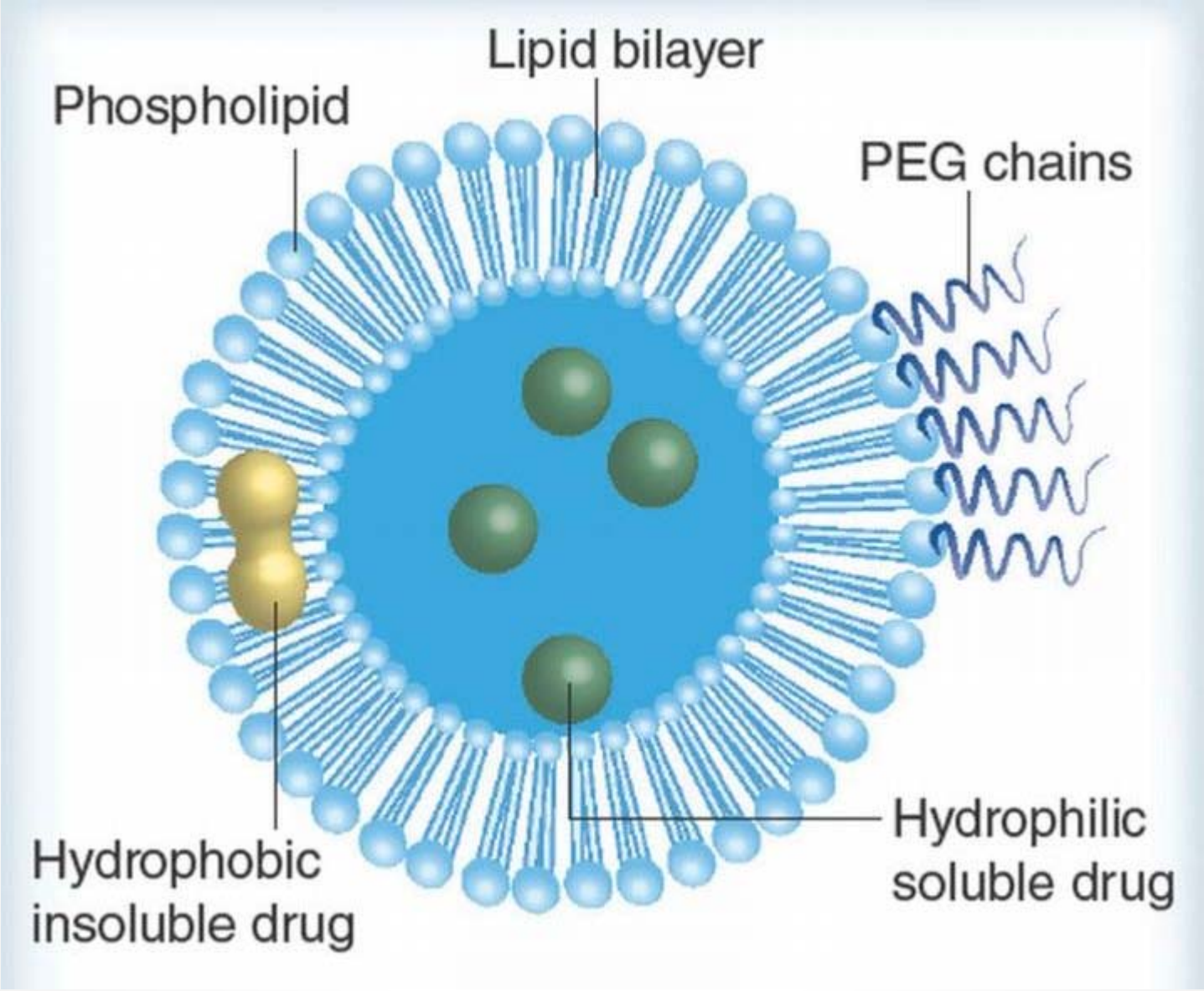
Lipoplatin





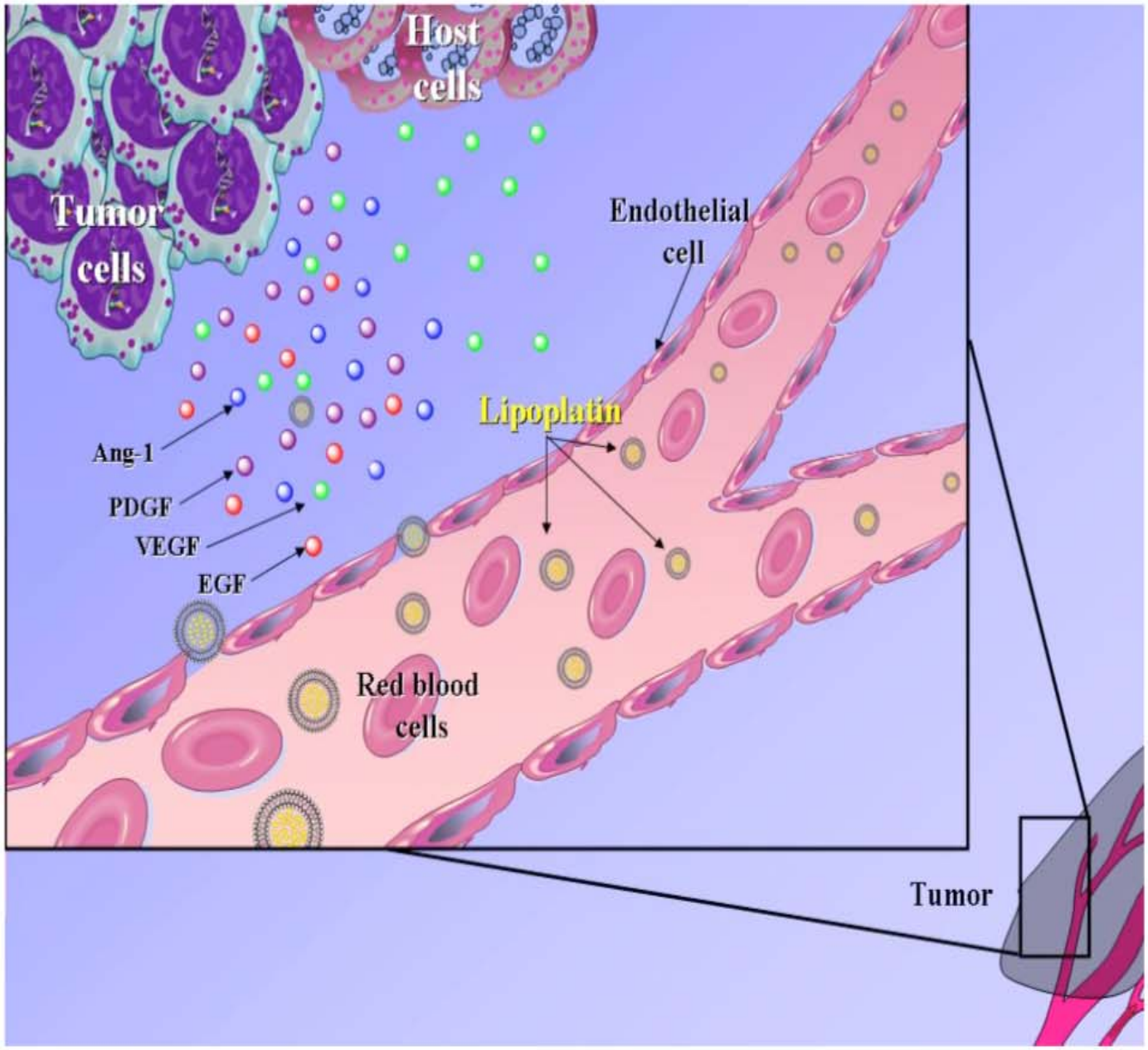
Lipoplatin molecule

Dipalmitoyl phosphatidyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol and methoxy- polyethylene glycol-distearoyl phosphatidyl-ethanolamine
(mPEG2000-DSPE)

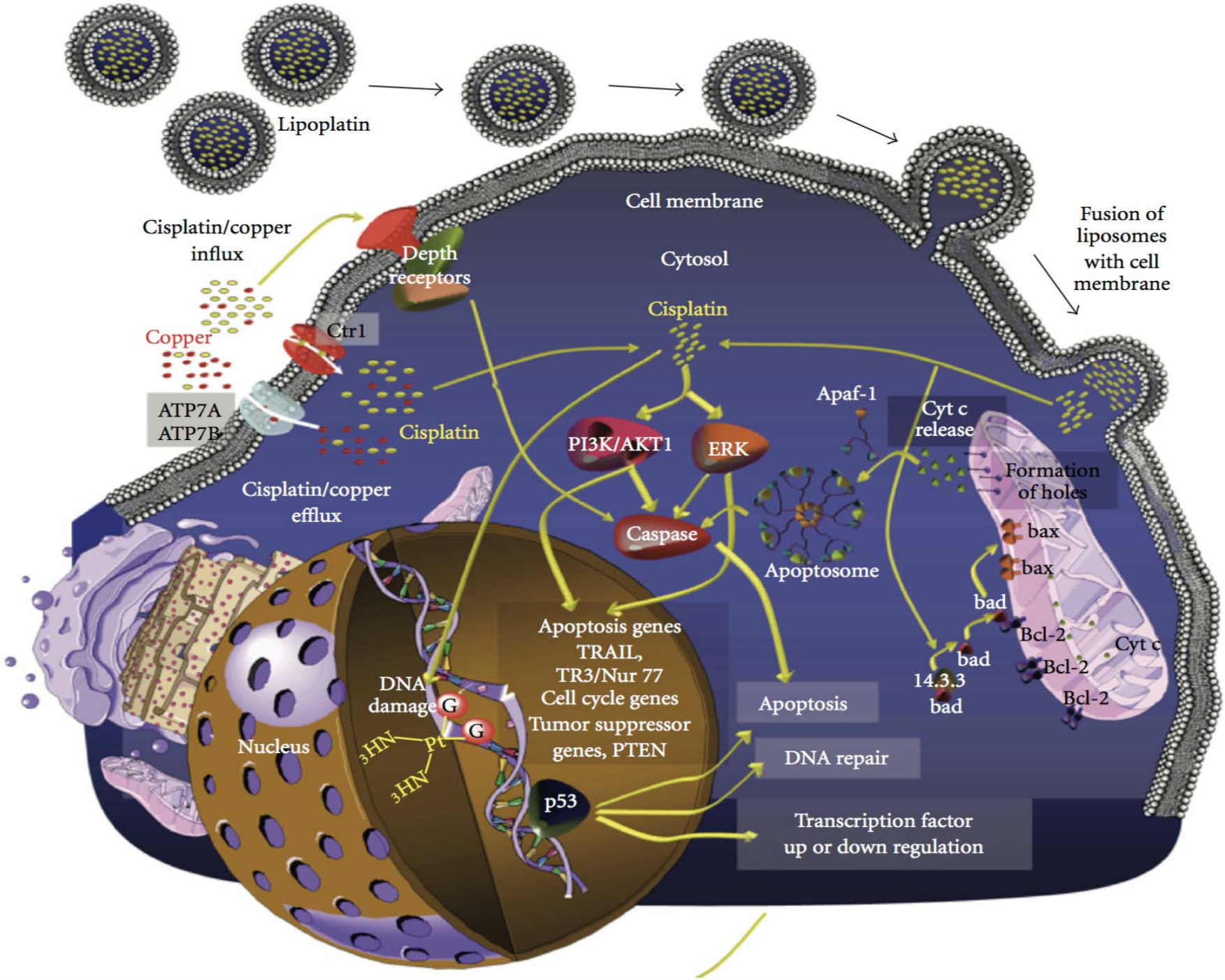

Lipid bilayer
Phospholipid
PEG chains
Hydrophobic
insoluble drug
Hydrophilic
soluble drug

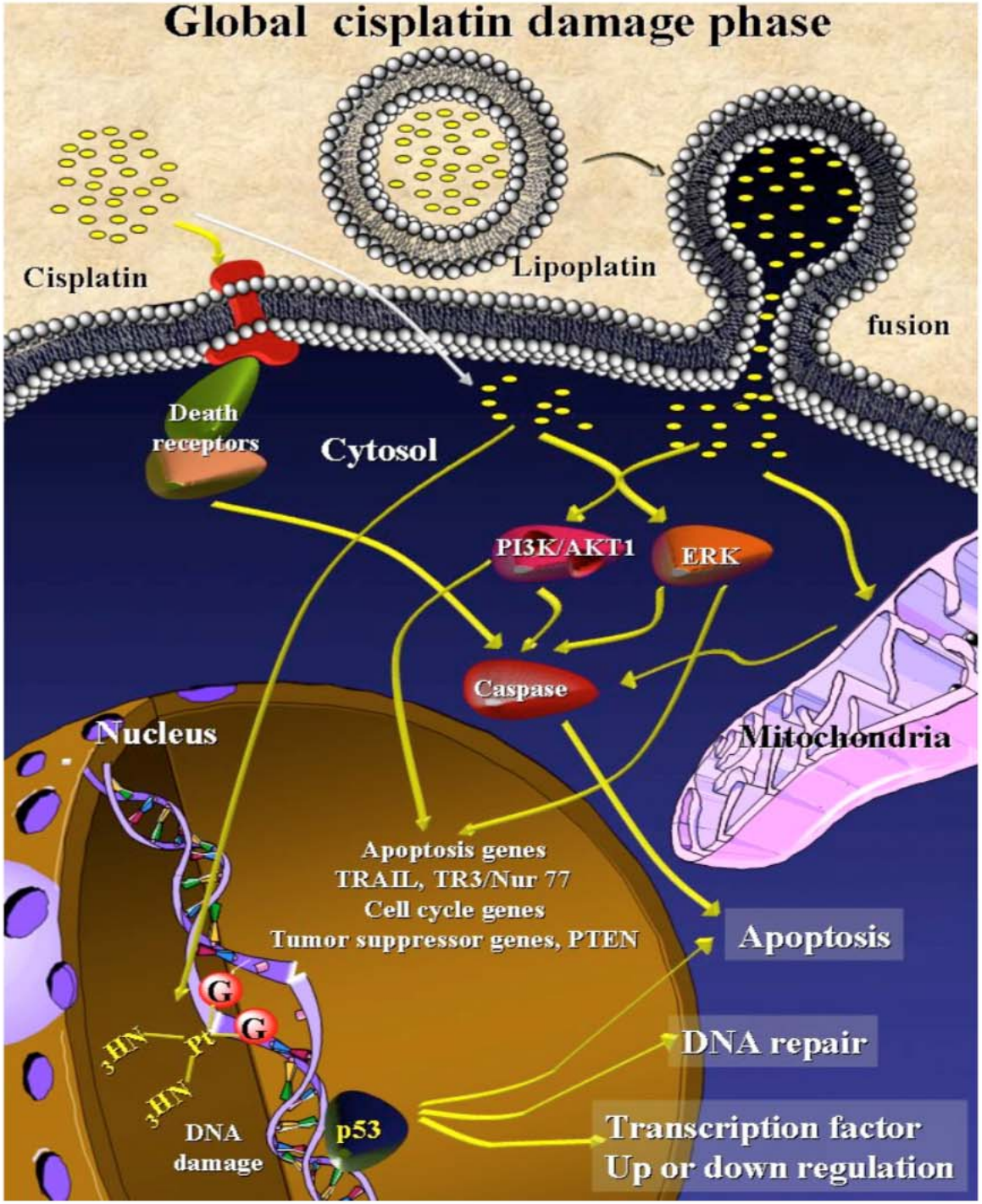
Lipoplatin

- **Liposomes contain**
  - 9% cisplatin
  - 91% lipid molecule

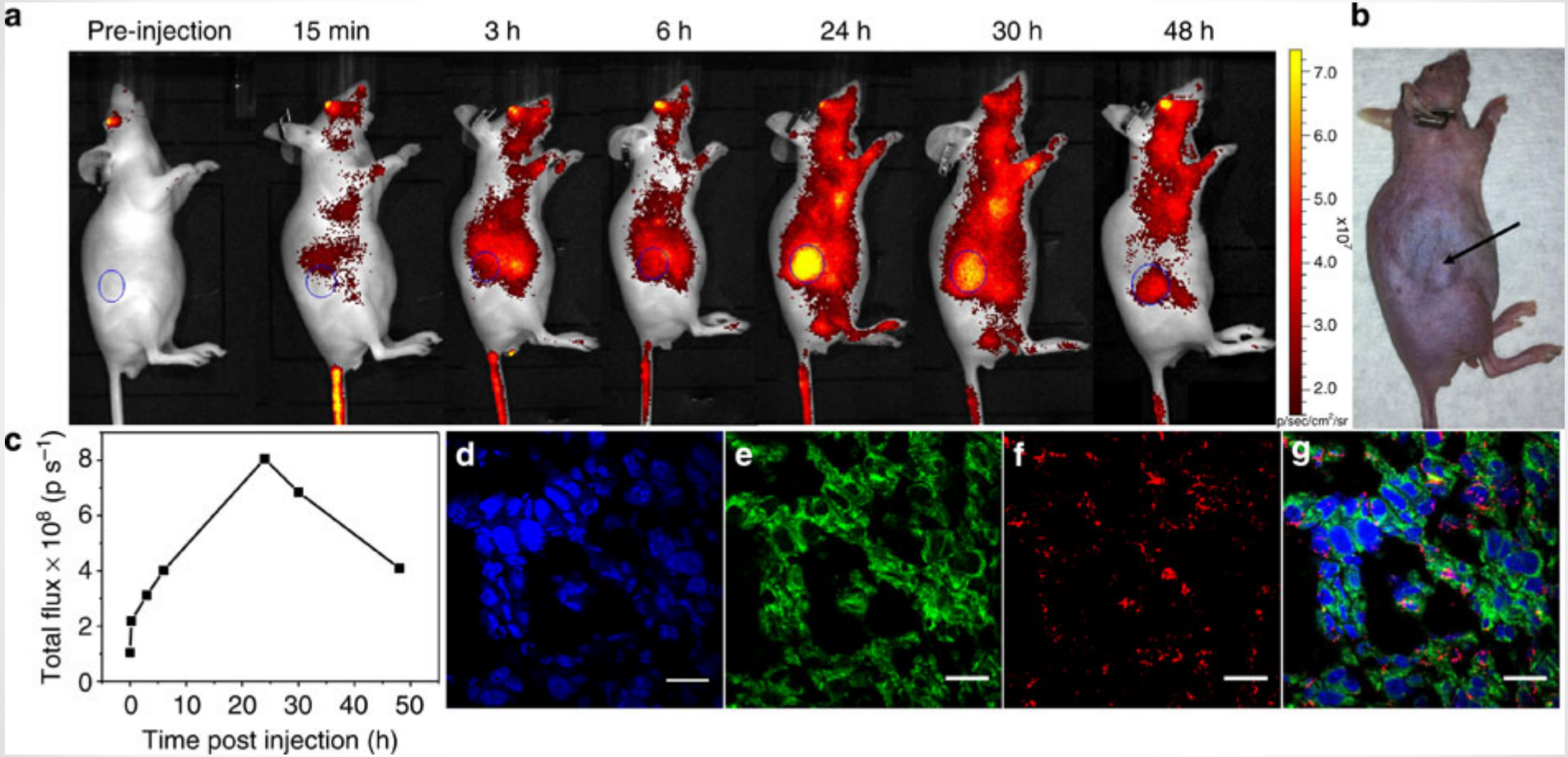


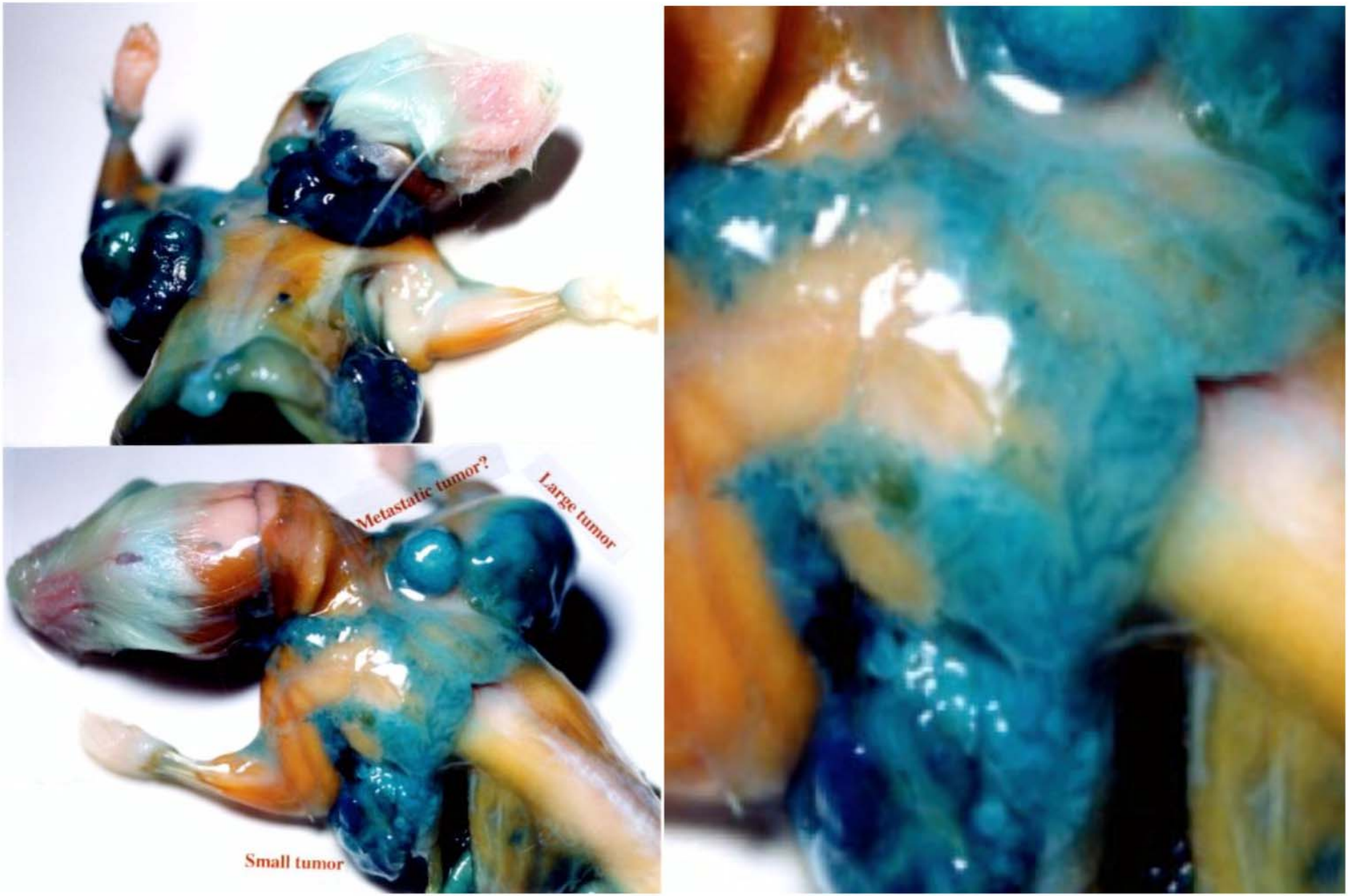
Lipoplatin nanoparticles extravasate preferentially through the compromised endothelium of the vasculature of the tumor.


Lipoplatin
Cell membrane
Cytosol
Fusion of liposomes with cell membrane
Cisplatin/copper influx
Depth receptors
Copper
Ctr1
ATP7A
ATP7B
Cisplatin
Cisplatin/copper efflux
Cisplatin
PI3K/AKT1
ERK
Caspase
Apaf-1
Cyt c release
Apoptosome
Formation of holes
bax
bax
bad
Bcl-2
Cyt c
bad
Bcl-2
14.3.3
bad
Bcl-2
Nucleus
DNA damage
G
G
3HN
Pt
3HN
Apoptosis genes
TRAIL,
TR3/Nur 77
Cell cycle genes
Tumor suppressor genes, PTEN
p53
Apoptosis
DNA repair
Transcription factor up or down regulation



Cisplatin induces a number of signaling pathways including the ERK pathway, the PI3K/AKT/PTEN and the Death pathway. These converge on Caspase activation and apoptosis. Activation of the PI3K/AKT pathway by cisplatin leads to the upregulation of proapoptotic genes such as TRAIL and of the tumor suppressor PTEN. Cisplatin also induces adduct and crosslinks in the DNA inducing p53 and the DNA damage repair versus DNA damage-induced apoptotic pathways. Lipoplatin is proposed to have a similar signaling activation effects on tumor cells.


a
Pre-injection
15 min
3 h
6 h
24 h
30 h
48 h
7.0
6.0
5.0
4.0
3.0
2.0
x10⁷
p/sec/cm²/sr
b
c
Total flux × 10⁸ (p s⁻¹)
8
6
4
2
0
0
10
20
30
40
50
Time post injection (h)
d
e
f
g



Targeting of the vasculature of the primary tumor and the metastases after systemic delivery of "Lipogenes" using our proprietary liposomal encapsulation technology. The photos (left) show a SCID mouse implanted with MCF-7 human breast tumor cells. Following systemic injection with the reporter β-galactosidase gene, the carcass was stained with X-Gal. Preferential staining of the tumors, especially of the vascular system around the tumors is evident (magnified picture to the right).

Lipoplatin

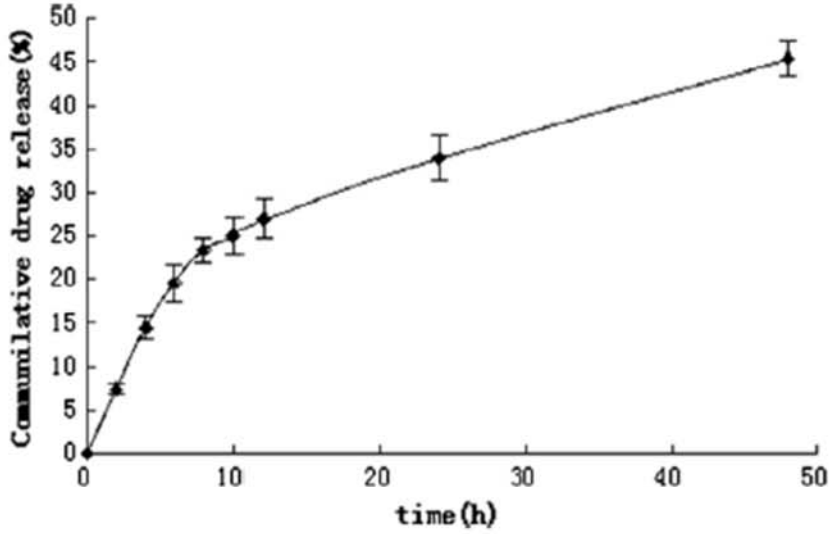


Fig. 3. Release profile of L-CDDP in PBS (pH 7.4, 0.15 M NaCl). Data are shown as the mean ± SD ($n = 3$).

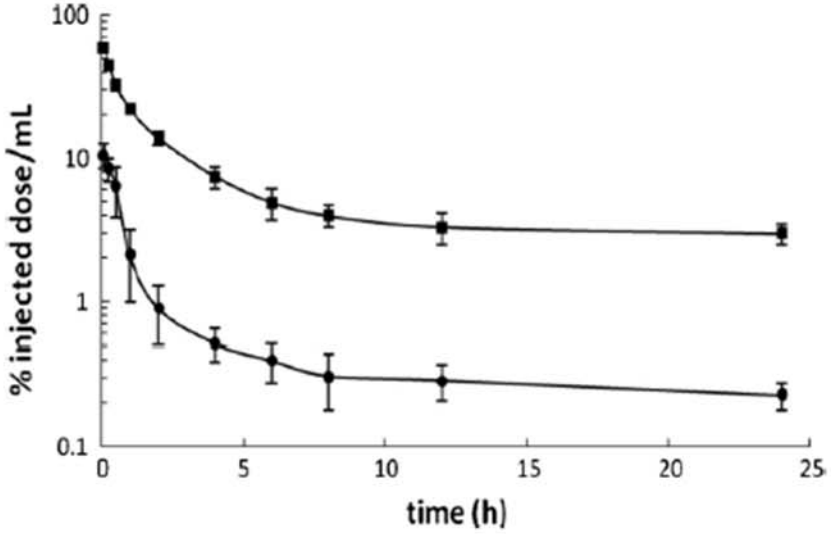


Fig. 4. Time profile of CDDP concentration in plasma after intravenous injection of free CDDP (●) and L-CDDP (■) at a dose of 6 mg CDDP/kg body weight ($n = 3$).

Table 1
Cytotoxicity of CDDP formulations in A549 cells.

IC_{50} (μM)	A549
CDDP	3.2 ± 0.2
L-CDDP	1.6 ± 0.5

Cytotoxicity was determined using MTT assay as described in Section 2. IC_{50} is the half maximal inhibitory concentration of CDDP.
Notes: Data are represented as the mean ± SD ($n = 3$).

Table 2
Survival of mice after treatment with CDDP and L-CDDP in A549 tumor-bearing mice[a].

Group	Treatment	Survival time (days)		% Increase life span		
		Range	Mean ± SE[b]	Median	Mean	Median
1	PBS	21–32	26 ± 5	23	–	–
2	CDDP	10–66	42 ± 19	40	62	74
3	L-CDDP	34–76	58 ± 15	53	123	130

[a] $n = 10$ for each treatment group.
[b] SE is the standard error of the mean.

Preclinical studies

- **Reduced side effect profile**
  - Tubular damage, nephrotoxicity and other adverse events caused by cisplatin in mice and rat studies were not observed with Lipoplatin
- **Advantage of delivering higher doses of drug**
  - Maximum Tolerable Dose of cisplatin in dogs is 70 mg/m2, whereas Lipoplatin can be administered with 150 mg/m^2 dose **without any prior hydration** and **without any toxicity**

Devarajan P, Tarabishi R, Mishra J, Ma Q, Kourvetaris A, Vougiouka M, and Boulikas T (**2004**) Low renal toxicity of Lipoplatin compared to cisplatin in animals. **Anticancer Res** 24, 2193-2200.

Lipoplatin

- Over 130 patients in 4 Phase-I studies
- Over 334 patients in 9 Phase-II studies
- Efficiency shown in NSCLC, gastric, breast, pancreas and bladder cancers
- Applied to EMA by 2 completed Phase-III studies for license authorization

Clinical studies

- Phase I – Lipoplatin dose escalation study
- Increased from 25 kg/m^2 to 125 mg/m^2
- 27 Stage 4 patients refractory to standard treatment (19 pancreas, 6 renal cell, 1 gastric, 1 head and neck squamous cell)
- Lipoplatin: second/third line, no pre/post-hidration
- Mild hematological and GI toxicity findings
- Nephrotoxicity, neurotoxicity, ototoxicity, hair loss, and other adverse events not observed

Stathopoulos GP, Boulikas T, Vougiouka M, Deliconstantinos G, Rigatos S, Darli E, Viliotou V, and Stathopoulos JG (**2005**) Pharmacokinetics and adverse reactions of a new liposomal cisplatin (Lipoplatin): Phase I study. **Oncol Rep** 13, 589-595.

Pharmacokinetics and adverse reactions of a new liposomal cisplatin (Lipoplatin): Phase I study (27 patients)

Stathopoulos et al, Oncol Rep, 13: 589-595 (2005)

Phase I-II trial of Lipoplatin (dose escalation) and Gemcitabine as a second-line chemotherapy in patients with advanced pancreatic cancer (24 patients)

Stathopoulos et al, Oncol Rep 15, 1201-1204 (2006)

Phase I trial of Lipoplatin (dose escalation) and Gemcitabine as a second-line chemotherapy in patients with non small cell lung carcinoma (13 patients)

Froudarakis et al, Cancer 113:2752-60 (2008)

Phase I study of Lipoplatin monotherapy: 350 mg/m2 DLT, MTD: 300 mg/m^2

Phase I study of Lipoplatin + paclitaxel. DLT: 250 mg/m^2 Lipoplatin; 175 mg/m^2 paclitaxel. MTD: 200 mg/m^2 Lipoplatin; 175 mg/m^2 paclitaxel (66 patients)

Stathopoulos et al, Liposomal cisplatin dose escalation for determining the maximum tolerated dose and dose-limiting toxicity: a phase I study. Anticancer Res. 30:1317-21 (**2010**).

Clinical studies

- Phase I / II – Lipoplatin+Gemcitabin dose escalation
- Pretreated advanced pancreas cancer
- Lipoplatin D1, D15, dose escalation, 100 mg/m^2 in most cases
- Every 4 weeks, minimum 3 cycles or until progression
- No neurotoxicity, nephrotoxicity, febrile neutropenia
- Grade 3-4 myelotoxicity with 125 mg/m^2 lipoplatin+1000 mg/m^2 gemcitabine
- **100 mg/m^2 Lipoplatin+1000 mg/m^2 gemcitabine, D1-D15, every 28 days, 3 cycles**

Stathopoulos GP, Boulikas T, Vougiouka M, Rigatos SK, Stathopoulos JG (**2006a**) Liposomal cisplatin combined with gemcitabine in pretreated advanced pancreatic cancer patients: a phase I-II study. **Oncol Rep** 15, 1201-1204.

Clinical studies

- Phase II – Lipoplatin+Gemcitabin
- First and second line chemoresistant pancreas, NSCLC, SCHN, bladder cancer
- 2-10 cycles
- No neuropathy, ototoxicity, hepatotoxicity, cardiotoxicity or allergic reaction
- Grade I-II nausea-vomiting in 4 patiens (%15,3)
- Myelotoxicity, Grade III in 1 patient, Grade I-II in 15 patients (%57,6)
- PR 8.3%, SD 58.3%, clinical benefit 66.6%

Stathopoulos GP, Boulikas T, Rigatos SK, Deliconstantinos G, Stathopoulos JG, Darli E, Viliotou V, Vougiouka M, Volakakis N (**2002**). Liposomal cisplatin combined with gemcitabine in pretreated advanced cancer patients. Phase I-II study **Annals of Oncology** 13 (Suppl. 5): page 25 (27th European Society for Medical Oncology Nice, France

PANCREATIC 1st line
EMEA orphan drug

Multicenter (registrational)
Lipoplatin 120mg/m^2 D 1,8,15 plus
Gemcitabine 1000mg/m^2 D 1,8
(21 days cycle)
ONGOING (30 pts)
5 Centers in GR

GI cancer 1st line

Dr. M. Koukourakis,
Univ. Hosp. of Alexandroupolis
Lipoplatin 120mg/m^2 D1 plus 5FU 400mg/m^2 D1 plus RT (4Gy D2,3 to the pelvis) weekly for 4 weeks against locally advanced GI adenocarcinoma
COMPLETED (12 pts)
Int. J. Radiation Oncology Biol. Phys. 2010 Sep 1;78(1):150-5

BREAST 1st line

American Univ. Hosp. Beirut, Lebanon
Lipoplatin 120 mg/m^2 D1, 8, 15 plus
Vinorelbine 30 mg/m^2 D1, 8
(HER2/neu-negative metastatic cancer)
COMPLETED (35 pts)
Farhat et al **2011** A Phase II Study of **Lipoplatin** (Liposomal Cisplatin)/Vinorelbine Combination in HER-2/neu-Negative Metastatic Breast Cancer. Clin Breast Cancer 11:384-9

NSCLC 1st line

Multicenter
Lipoplatin 120mg/m^2 D 1,8,15 plus
Gemcitabine 1000mg/m^2 D 1,8
(21 days cycle)
vs cisplatin-gemcitabine
COMPLETED (88 pts)
Mylonakis et al Lung Cancer. 2010 68:240-7.

NSCLC 2nd or 3rd line

Lipoplatin monotherapy 200mg/m2 D 1,2
Every 14 days up to 6 cycles
Ongoing (21 pts)
Stathopoulos et al

Urinary & NSCLC

Patients with renal insufficiency. It shows the safety and efficacy of Lipoplatin for treating this group (40 patients)
Stathopoulos et al ASCO 2011

PHASE II
>334 pts

NSCLC 1st line

Lipoplatin monotherapy 200mg/m^2 D 1
Every 14 days up to 6 cycles
With Oncothermia
Ongoing (20 pts by Ap 2012)
Slavin et al, ISRAEL

NSCLC 1st line

Lipoplatin monotherapy 120mg/m2 D 1
Every 7 days up to 6 cycles
With weekly fractions of RT
Ongoing (40 pts by Ap 2012)
Dr. M. Koukourakis,
Univ. Hosp. of Alexandroupolis

NSCLC 2nd line in Pt-treated patients

Lipoplatin 120mg/m^2 D 1,8 plus
Gemcitabine 1000mg/m^2 D 1,8
(21 days cycle)
COMPLETED (48 pts)
Dr. Froudarakis, Alexandroupolis University Hospital

Clinical studies

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

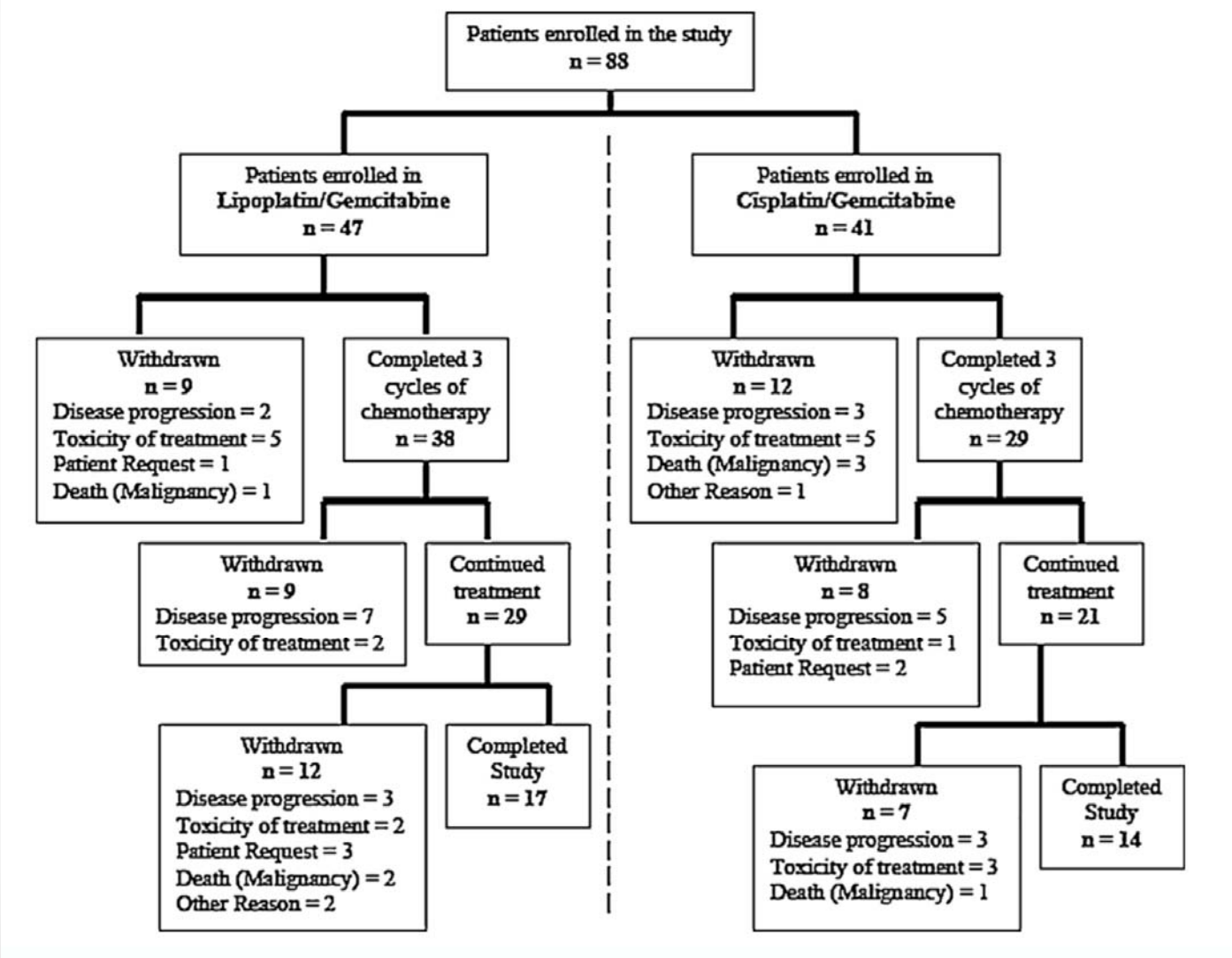
Phase II study of liposomal cisplatin (Lipoplatin™) plus gemcitabine versus cisplatin plus gemcitabine as first line treatment in inoperable (stage IIIB/IV) non-small cell lung cancer

N. Mylonakis[a], A. Athanasiou[b], N. Ziras[b], J. Angel[c], A. Rapti[d], S. Lampaki[e], N. Politis[f], C. Karanikas[a], C. Kosmas[a,*]

[a] *2nd Department of Medical Oncology, "Metaxa" Cancer Hospital, 51 Botassi Street, 18537 Piraeus, Greece*
[b] *1st Department of Medical Oncology, "Metaxa" Cancer Hospital, Piraeus, Greece*
[c] *Pulmonary Medicine Department, "Theageneio" Anticancer Hospital, Thessaloniki, Greece*
[d] *8th Pulmonary Clinic, "Sotiria" Chest Diseases Hospital, Athens, Greece*
[e] *Department of Medical Oncology, Aristotle University of Thessaloniki School of Medicine Papageorgiou Hospital, Thessaloniki, Greece*
[f] *Pulmonary Medicine Clinic, "Agios Savvas" Anticancer Hospital, Athens, Greece*

Clinical studies

- Phase II – Lipoplatin+Gemcitabin



Clinical studies

Patient demographics.

Parameter	Lipoplatin–gemcitabine	Cisplatin–gemcitabine
No. of Patients(n)	47	41
Male/female	45/2	33/8
Median age [years (range)]	64 (49–83)	66 (52–77)
Histological type [patients (%)]		
Adenocarcinoma	21 (45)	24 (59)
Squamous cell carcinoma	15 (32)	10 (24)
Large cell carcinoma	1 (2)	7 (17)
Low-differentiated NSCLC	10 (21)	0 (0)
Disease stage [patients (%)]		
I–IIIA (inoperable)	1 (2)	7 (17)
IIIB	15 (30)	7 (17)
IV	32 (68)	27 (66)
ECOG performance status [patients (%)]		
0	27 (57)	24 (59)
1	20 (43)	16 (39)
2	0 (0)	1 (2)
No. of metastatic sites (%)		
Median	1	1
0	16 (34)	14 (34)
1	11 (23)	15 (36)
2	6 (13)	8 (20)
3	4 (9)	2 (5)
4 or more	10 (21)	2 (5)
Previous treatments [patients (%)]		
Radiotherapy	9 (19)	4 (10)
Surgery	10 (21)	3 (7)
Radiotherapy and surgery [patients (%)]	2 (4)	3 (7)

Clinical studies

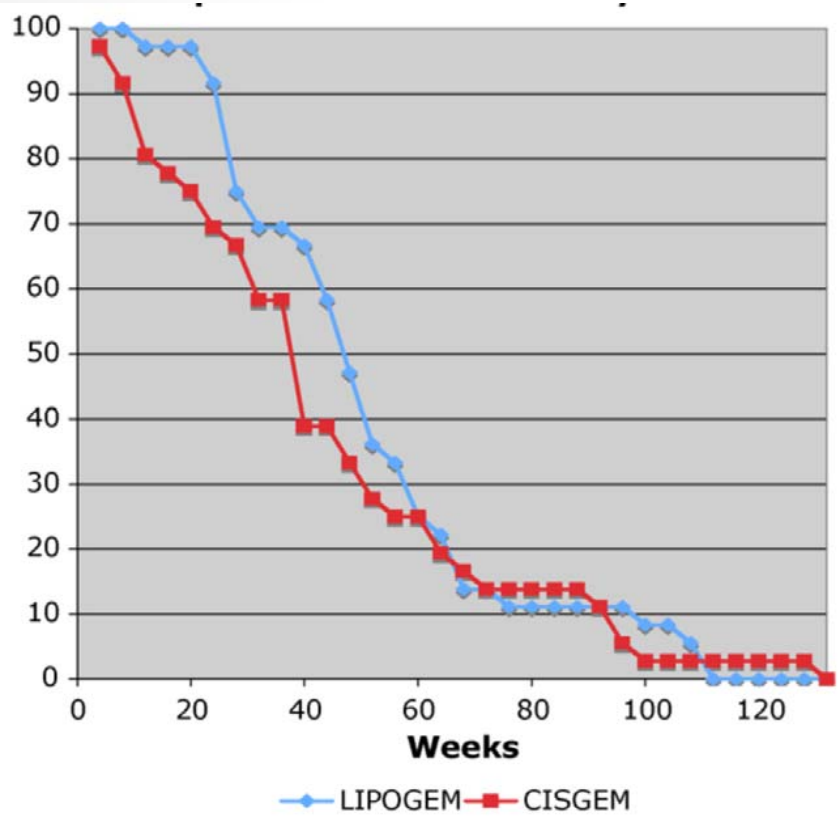
Efficacy data of Lipoplatin + gemcitabine versus cisplatin + gemcitabine treatments.

Parameter	Arm A, LipoGem	Arm B, CisGem
No. of Patients (*n*)	47	41
Evaluable (%)	41 (87)[a]	39 (95) [a]
Non-evaluable (%)	6 (13)[b]	2 (5) [b]
Complete response	0 (0%)	0 (0%)
Partial response	13 (31.7%)	10 (25.6%)
Objective response rate [% (95% CI)]	13 (31.7%) [21.5–51.6]	10 (25.6%) [13.8–42.6]
Stable disease	16 (39%)	12 (30.8%)
Disease control rate [% (95% CI)]	29 (70.7%) [56.5–84.9]	22 (56.4%) [43.2–74.7]
Progressive disease	12 (29.3%)	17 (43.6%)
Median PFS [months (range)]	– (0.7–16.8+)[c]	– (0.2–9.8+)[c]
Median duration of response [months (range)]	– (2.8–14.8+)[d]	– (2.1–10.4+)[d]
CI 95% for PFS	6	6
Median OS [months (range)]	– (1.3–17.0+)[e]	– (1.0–16.5+)[e]
CI 95% for OS	8	10
1-year survival	30%	24%

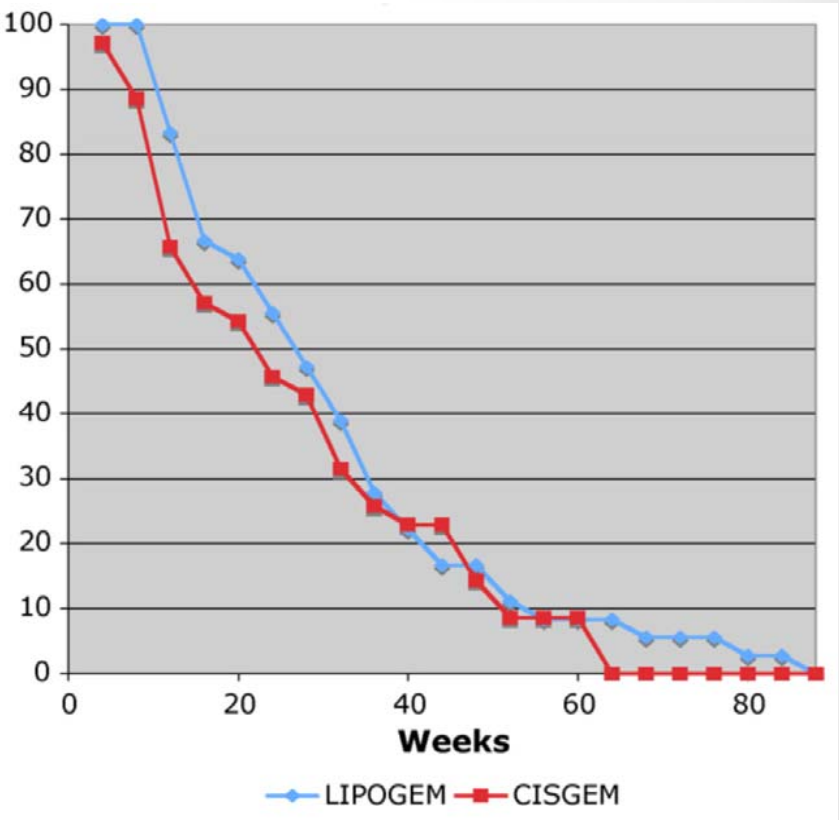
ORR	32%	26%
Clinical benefit	71%	57%
1 year OS	30%	24%

Clinical studies

OS



PFS



Clinical studies

Grade 3

Grade 4

WHO-TC category term	LipoGem grade 3, *n* (%)	CisGem grade 3, *n* (%)	LipoGem grade 4, *n* (%)	CisGem grade 4, *n* (%)
Anaemia	1 (2)	4 (10)	0 (0)	0 (0)
Leukopenia	4 (9)	3 (7)	0 (0)	4 (10)
Neutropenia	4 (9)	7 (17)	1 (2)	5 (12)
Thrombocytopenia	4 (9)	5 (12)	0 (0)	4 (10)
Creatinine	0 (0)	2 (5)	0 (0)	0 (0)
Transaminases/bilirubin	2 (4)	6 (15)	0 (0)	1 (2)
Nausea/vomiting	1 (2)	5 (12)	0 (0)	0 (0)
Infection	1 (2)	0 (0)	0 (0)	0 (0)
Fever of unknown origin	0 (0)	1 (2)	0 (0)	0 (0)
Allergy	0 (0)	0 (0)	0 (0)	0 (0)
Alopecia	1 (2)	1 (2)	0 (0)	0 (0)
Sensory/motor	0 (0)	2 (5)	0 (0)	0 (0)
Asthenia	2 (4)	7 (17)	0 (0)	0 (0)
Anorexia	1 (2)	6 (15)	0 (0)	0 (0)
Metallic taste	0 (0)		0 (0)	

Clinical studies

Grade		Arm	
		Arm A, LipoGem infusion number (%)	Arm B, CisGem infusion number (%)
I	Nephrotoxicity (p-value <0.001)	74 (13)	44 (19.6)
II		8 (1.4)	10 (4.5)
III		1 (0.2)	2 (0.9)
IV		0 (0)	0 (0)
Total		83/569 (**14.6**)	56/224 (**25**)
I	Leukopenia (p-value = 0.009)	33 (5.9)	17 (5.7)
II		10 (1.8)	15 (5)
III		3 (0.5)	3 (1)
IV		0 (0)	3 (1)
Total		46/558 (**8.2**)	38/300 (**12.7**)
I	Thrombocytopenia (p-value = 0.065)	77 (14.3)	55 (18)
II		8 (1.5)	9 (2.9)
III		6 (1.1)	4 (1.3)
IV		1 (0.2)	4 (1.3)
Total		92/537 (**17.1**)	72/306 (**23.5**)
I	Anaemia (p-value = 0.699)	354 (64.5)	192 (62.1)
II		52 (9.5)	36 (11.7)
III		2 (0.4)	2 (0.6)
IV		0 (0)	0 (0)
Total		408/549 (74.3)	203/309 (74.4)
I	Nausea & Vomiting (p-value < 0.001) numbers denote patients, not infusions	18 (38)	10 (24)
II		4 (9)	18 (44)
III		1 (2)	5 (12)
IV		0 (0)	0 (0)

Clinical studies

- Other Phase-II Studies

NSCLC

- **Lipoplatin monotherapy**
- **Lipoplatin+Gemcitabine**

Metastatic Breast Cancer

- **Lipoplatin+Docetaxel**
- **Lipoplatin+Navelbin**

Metastatic Gastric Cancer

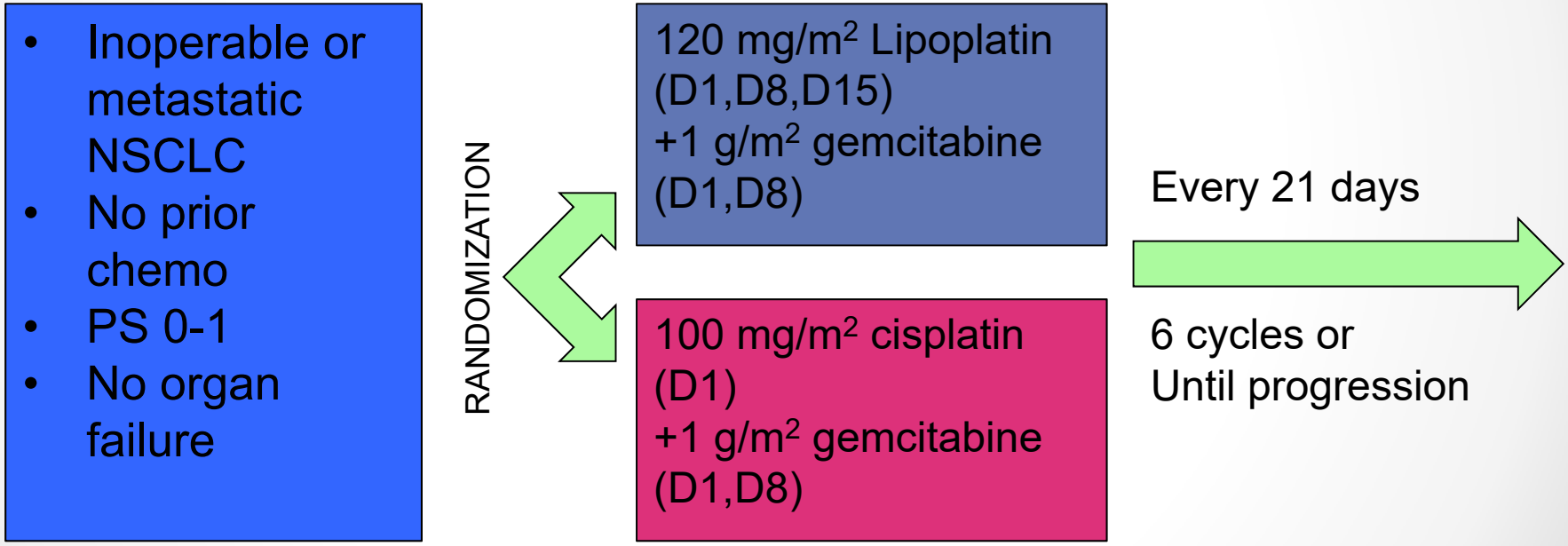
- **Lipoplatin+5-FU+RT**

Head and Neck Cancer

- **Lipoplatin+RT**

Clinical studies

- Phase-III: LipoGEM



Boulikas T, Mylonakis N, Sarikos G, Angel J, Athanasiou A, Politis G, Rapti A, Rassidakis A, Karabatzaki M, Anyfantis N (**2007**) Lipoplatin plus gemcitabine versus cisplatin plus gemcitabine in NSCLC: Preliminary results of a phase III trial. **J Clin Oncol**, 2007 ASCO Annual Meeting Proceedings Part I. 25, 18028

Clinical studies

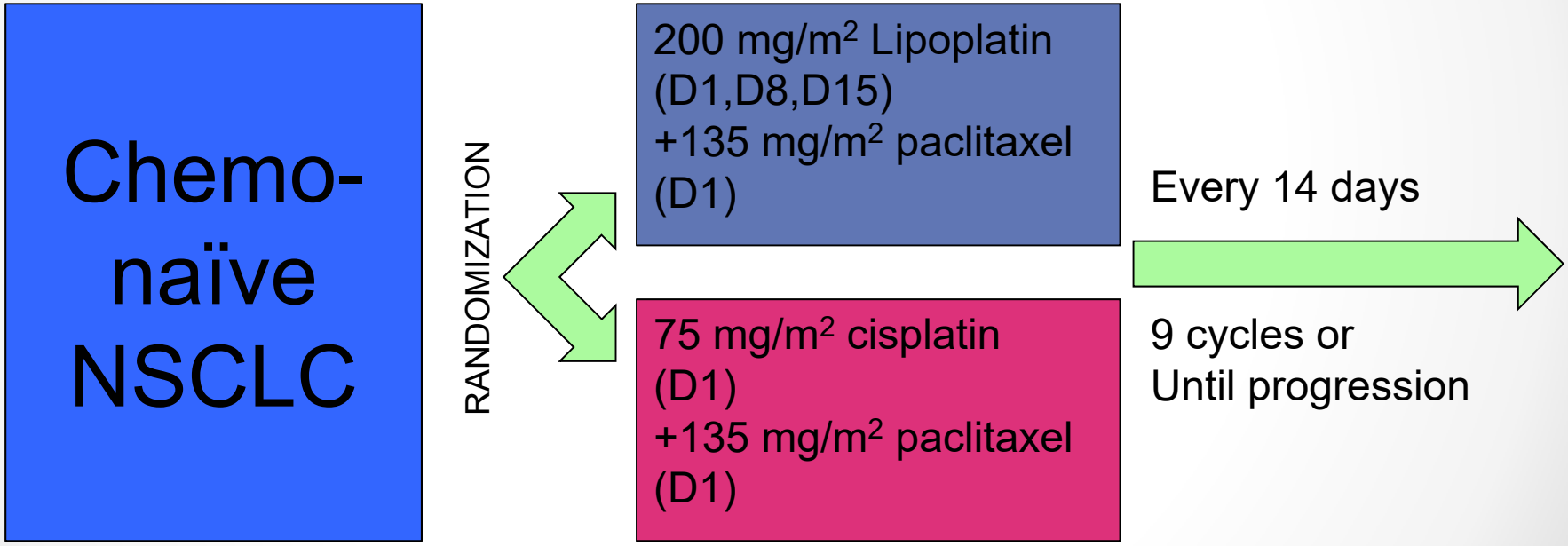
- Phase-III: LipoGEM

	120 mg/m^2 Lipoplatin +1 g/m^2 gemcitabine (n=33)	100 mg/m^2 cisplatin +1 g/m^2 gemcitabine (n=26)
PR	4 patients	4 patients
SD	23%	12%
PD	16%	35%
Nephrotoxicity	Grade II, 6%	Grade II, 19%
Neutropenia	Grade III, 3%	Grade III, 15%
Hepatotoxicity	38%	46%

Boulikas T, Mylonakis N, Sarikos G, Angel J, Athanasiou A, Politis G, Rapti A, Rassidakis A, Karabatzaki M, Anyfantis N (**2007**) Lipoplatin plus gemcitabine versus cisplatin plus gemcitabine in NSCLC: Preliminary results of a phase III trial. **J Clin Oncol**, 2007 ASCO Annual Meeting Proceedings Part I. 25, 18028

Clinical studies

- Phase-III: LipoTaxol



Stathopoulos GP, Michalopoulou P, Antoniou D, Dimitroulis J, Giamboudakis P, Marosis K, Stathopoulos J, Tsoukalas G, Grigoratou T (**2007**). Liposomal cisplatin and paclitaxel versus cisplatin and paclitaxel in advanced NSCLC. **J Clin Oncol**, 2007 ASCO Annual Meeting Proceedings Part I. 25, 7684

Clinical studies

- Phase-III: LipoTaxol

	200 mg/m^2 Lipoplatin +135 mg/m^2 paclitaxel (n=27)	75 mg/m^2 cisplatin +135 mg/m^2 paclitaxel (n=27)
PR	48.2%	44.4%
SD	37.0%	44.4%
PD	3.7%	3.7%
Clinical benefit	85%	88%
Nephrotoxicity	3.7%	25.9%
Neurotoxicity	Grade I-II, 25.9%	Grade I-III, 44.4%
Nausea-vomiting	18.5%	25.9%
Myelotoxicity	Grade I-II, 37.0%	Grade I-III, 63.0%

Stathopoulos GP, Michalopoulou P, Antoniou D, Dimitroulis J, Giamboudakis P, Marosis K, Stathopoulos J, Tsoukalas G, Grigoratou T (**2007**). Liposomal cisplatin and paclitaxel versus cisplatin and paclitaxel in advanced NSCLC. **J Clin Oncol**, 2007 ASCO Annual Meeting Proceedings Part I. 25, 7684

SCCHN

Lipoplatin 100 mg/m^2/d Day$_{1,8,15}$
plus 5-FU 1000 mg/m^2/d Day $_{1-5}$
versus
Cisplatin 100 mg/m^2/d Day$_1$ plus
5-FU 1000 mg/m^2/d Day$_{1-5}$
21 days cycle
6 cycles/PD
ONGOING (110 pts)
Jehn et al AR. 2007: 27:471-5
Jehn et al AR. 2008, 28:3961-4

NSCLC 1st line

Lipoplatin 120mg/m^2 D$_{1,8,15}$ plus
Gemcitabine 1000mg/m^2 D$_{1,8}$
versus
Cisplatin 100mg/m^2 D$_1$ plus
Gemcitabine 1000mg/m^2 D$_{1,8}$
21 days cycle
6 cycles/PD
ONGOING (>220 pts)

NSCLC 1st line
Adenocarcinoma

Lipoplatin 200 mg/m^2 Day$_{1,8}$
plus Pemetrexed 500 mg/m^2
Day$_1$ versus
Cisplatin 75 mg/m^2 Day$_1$ plus
Pemetrexed 500 mg/m^2 Day$_1$
21 days cycle, 6 cycles/PD
Ongoing
84 Centers in GR, DE, IT, FR,
UK, PO, RO, ES, SE, TW, TR,
IL, CN, RU, CA, AU, US

PANCREATIC 1st line

EMEA orphan drug
Multicenter (registrational)
Lipoplatin 200mg/m^2 D1,8 plus
Gemcitabine 1000mg/m^2 D 1,8
(21 days cycle)
ONGOING
53 Centers in GR, DE, IT, FR, UK,
PO, RO, ES,
TW, TR, IL, CN, RU, CA, AU,
US

Phase III
768 pts

NSCLC 1st line

Lipoplatin 200mg/m^2 D$_1$ plus
Paclitaxel 135mg/m^2 D$_1$
versus
Cisplatin 75mg/m^2 D$_1$ plus
Paclitaxel 135mg/m^2 D$_1$
14 days cycle
9 cycles/PD
COMPLETED (236 pts)
Stathopoulos et al; Annals of
Oncology, 2010 21:2227-32

GASTRIC

Lipoplatin 120mg/m^2 D$_1$ plus
5-FU 400mg/m^2 D$_1$ and Radiation
of a 7 day cycle
versus
Cisplatin 75mg/m^2 D$_1$ plus
5-FU 400mg/m^2 D$_1$ and Radiation
of a 21 day cycle
PLANNED

Non-squamous NSCLC 1st line

Lipoplatin 200mg/m^2 D$_1$ plus
Paclitaxel 135mg/m^2 D$_1$
Versus Cisplatin 75mg/m^2 D$_1$
plus Paclitaxel 135mg/m^2 D$_1$
14 days cycle, 9 cycles/PD
COMPLETED (202 pts)
Stathopoulos et al; Cancer
Chemother Pharmacol. 2011
68:945–950

Toxicity

Table 2: Toxicity: lipoplatin monotherapy.

Dosage lipoplatin mg/m^2	Toxicity	Grade 1 n	2 n	3 n	4 n
150–250	Nausea-vomiting	—	—	—	—
	Fatigue	—	—	—	—
	Diarrhea	—	—	—	—
	Nephrotoxicity	—	—	—	—
	Neutropenia	—	—	—	—
	Neurotoxicity	—	—	—	—
300	Nausea-vomiting	2/4	1/4	—	—
	Fatigue	2/4	1/4	—	—
	Neutropenia	1/4	—	—	—
	Nephrotoxicity	1/4	—	—	—
350	Nausea-vomiting	1/4	3/4	—	—
	Fatigue	1/4	3/4	—	—
	Neutropenia	2/4	1/4	1/4	—
	Nephrotoxicity	2/4	1/4	1/4	—

Lipoplatin vs. Cisplatin

- More efficient?
- Patient numbers
- Lower toxicity
- Tolerable adverse event profile
- Lipoplatin is a very efficient molecule in epithelial malignancies (85% of all cancers)

Lipoplatin vs. Platin Drugs

Regimen	Partial response in lung adenocarsinomas (PR)	Nephrotoxicity	Myelotoxicity	Neurotoxicity	GI toxicity
Cisplatin + Paclitaxel	PR 42%	+++	+++	++	+++
Carboplatin + Paclitaxel (popular in USA)	~30%	+	++++	+	+
Oxaliplatin+ Paclitaxel	~30%	+	+	+++	++
Lipoplatin+ Paclitaxel	PR 59%	+	+	+	+
Cisplatin + gemcitabine (popular in EU)	PR 25%	+++	+++	++	+++
Lipoplatin+ gemcitabine	PR 44%	+	++	+	+

Current Research Topics
Lipoplatin+RT

Anticancer Res. 2013 Aug;33(8):3005-14.

Efficacy of cisplatin and Lipoplatin™ in combined treatment with radiation of a colorectal tumor in nude mouse.

Tippayamontri T[1], Kotb R, Paquette B, Sanche L.

Author information

Abstract

BACKGROUND: Optimal conditions for efficient concomitant chemoradiation treatment of colorectal cancer with cisplatin still need to be better defined. In addition, intolerance of healthy tissue to cisplatin prevents the full exploitation of its radiosensitizing potential. A liposomal formulation of cisplatin, Lipoplatin™, was proposed to overcome its toxicity. Using an animal model of colorectal cancer, we determined the platinum window, defined by studying the pharmacokinetics and time-dependent intracellular distribution of cisplatin and Lipoplatin™.

MATERIALS AND METHODS: In nude mice bearing HCT116 human colorectal carcinoma treated with cisplatin or Lipoplatin™, the platinum accumulation in blood, serum, different normal tissues, tumor and different tumor cell compartments was measured by inductively coupled plasma mass spectrometry. Radiation treatment (15 Gy) was given 4, 24, and 48 h after drug administration and was correlated to the amount of platinum-DNA adducts in the cancer cells. The resulting tumor growth delay is reported and correlated to apoptosis analysis.

RESULTS: The greatest effects and highest apoptosis were observed when radiation was given at 4 h or 48 h after drug injection. These times correspond to the times of maximal platinum binding to tumor DNA. An enhancement factor (ratio of group treated by combined treatment compared to chemotherapy alone) of 13.00 was obtained with Lipoplatin™, and 4.09 for cisplatin when tumor irradiation was performed 48 h after drug administration.

CONCLUSION: The most efficient combination treatment of radiation with cisplatin or Lipoplatin™ was observed when binding of platinum to DNA was highest. These results improve our understanding over the mechanisms of platinum-induced radiosensitization and should have significant impact on the design of more efficient treatment protocols.

KEYWORDS: Lipoplatin™; Radiotherapy; chemotherapy; cisplatin; colorectal cancer; concomitant therapy

Current Research Topics
Metastatic Breast CA

Clin Breast Cancer. 2011 Dec;11(6):384-9. doi: 10.1016/j.clbc.2011.08.005. Epub 2011 Oct 10.

A phase II study of lipoplatin (liposomal cisplatin)/vinorelbine combination in HER-2/neu-negative metastatic breast cancer.

Farhat FS[1], Temraz S, Kattan J, Ibrahim K, Bitar N, Haddad N, Jalloul R, Hatoum HA, Nsouli G, Shamseddine AI.

Author information

Abstract

We assessed the efficacy and safety of a liposomal cisplatin (lipoplatin) and vinorelbine combination in metastatic breast cancer (MBC). Thirty-five patients were treated. The objective response rate was 53.1% and the median survival time was 22 months. Grade 3/4 neutropenia was observed in 44% of cycles, and febrile neutropenia was seen in 4 patients (11.4%). No grade 3/4 nephrotoxicity or neuropathy was noted. This combination is effective and well tolerated in patients with MBC and it warrants investigation as first-line treatment.

BACKGROUND: Liposomal cisplatin (lipoplatin) has a mechanism of action similar to that of cisplatin, with reduced toxicities and enhanced or similar efficacy. We wanted to assess the efficacy and safety of a lipoplatin/vinorelbine combination in a phase II clinical trial in metastatic breast cancer (MBC).

METHODS: Thirty-five patients with HER-2/neu-negative (HER-2/neu(-)) MBC were enrolled. Lipoplatin 120 mg/m(2) (days 1, 8, and 15) and vinorelbine 30 mg/m(2) (days 1 and 8) were administered in a 21-day cycle.

RESULTS: Thirty-five patients were included in the intent-to-treat (ITT) analysis; 32 patients were evaluable for response. The objective response rate was 53.1%. Complete response (CR) was achieved in 3 patients (9.4%), partial response (PR) was seen in 14 patients (43.8%), stable disease (SD) was obtained in 12 patients (37.5%), and progressive disease (PD) was seen in 3 patients (9.4%). Median time to disease progression was 8 months (range 6-10 months). After a median follow-up of 15.5 months, 18 patients were still alive; the median survival time was 22 months (95% confidence interval [CI], 14-30). A total of 174 cycles were administered. Neutropenia was the most frequent hematologic toxicity, with grade 3/4 neutropenia observed in 44% of cycles. Febrile neutropenia was observed in 4 patients (11.4%). No grade 3/4 nephrotoxicity or neuropathy was noted. Grade 1/2 nephrotoxicity occurred in 8 patients (22.9%) and grade 3 vomiting was seen in 3 patients (8.6%).

CONCLUSIONS: The results of this trial reveal that vinorelbine/lipoplatin is effective in treating patients with MBC. This regimen is well tolerated with no grade 3/4 nephrotoxicity or neuropathy. The investigation of this regimen as first-line treatment in MBC is warranted.

Current Research Topics

Ovarian CA

Preclinical Activity of the Liposomal Cisplatin Lipoplatin in Ovarian Cancer

Naike Casagrande[1], Marta Celegato[1], Cinzia Borghese[1], Maurizio Mongiat[1], Alfonso Colombatti[1,2], and Donatella Aldinucci[1]

Abstract

Purpose: Cisplatin and its platinum derivatives are first-line chemotherapeutic agents in the treatment of ovarian cancer; however, treatment is associated with tumor resistance and significant toxicity. Here we investigated the antitumoral activity of lipoplatin, one of the most promising liposomal platinum drug formulations under clinical investigation.

Experimental Design: *In vitro* effects of lipoplatin were tested on a panel of ovarian cancer cell lines, sensitive and resistant to cisplatin, using both two-dimensional (2D) and 3D cell models. We evaluated *in vivo* the lipoplatin anticancer activity using tumor xenografts.

Results: Lipoplatin exhibited a potent antitumoral activity in all ovarian cancer cell lines tested, induced apoptosis, and activated caspase-9, -8, and -3, downregulating Bcl-2 and upregulating Bax. Lipoplatin inhibited thioredoxin reductase enzymatic activity and increased reactive oxygen species accumulation and reduced EGF receptor (EGFR) expression and inhibited cell invasion. Lipoplatin demonstrated a synergistic effect when used in combination with doxorubicin, widely used in relapsed ovarian cancer treatment, and with the albumin-bound paclitaxel, Abraxane. Lipoplatin decreased both ALDH and CD133 expression, markers of ovarian cancer stem cells. Multicellular aggregates/spheroids are present in ascites of patients and most contribute to the spreading to secondary sites. Lipoplatin decreased spheroids growth, vitality, and cell migration out of preformed spheroids. Finally, lipoplatin inhibited more than 90% tumor xenograft growth with minimal systemic toxicity, and after the treatment suspension, no tumor progression was observed.

Conclusion: These preclinical data suggest that lipoplatin has potential for clinical assessment in aggressive cisplatin-resistant patients with ovarian cancer. *Clin Cancer Res; 20(21); 5496–506. ©2014 AACR.*

Current Research Topics

Cisplatin-Resistant Cervical CA

Gynecol Oncol. 2013 Dec;131(3):744-52. doi: 10.1016/j.ygyno.2013.08.041. Epub 2013 Sep 10.

Preclinical evaluation of a new liposomal formulation of cisplatin, lipoplatin, to treat cisplatin-resistant cervical cancer.

Casagrande N[1], De Paoli M, Celegato M, Borghese C, Mongiat M, Colombatti A, Aldinucci D.

Author information

Abstract

OBJECTIVE: Cisplatin-based chemotherapy has been shown to improve survival in cervical cancer; however, treatment is associated with tumor resistance and significant toxicity. Lipoplatin is a new liposomal formulation of cisplatin, developed to reduce cisplatin toxicity, to improve drug accumulation at tumor sites and to overcome drug resistance. The aim of this study is to analyze the antitumoral activity of lipoplatin against cisplatin-resistant cervical cancer cells and to investigate its mechanism of action.

METHODS: The activity and mechanism of action of lipoplatin were studied in the ME-180 cervical cancer cell line and its cisplatin-resistant clone R-ME-180 and HeLa cells using cell proliferation assays, flow cytometry, ELISA assay, cell migration, spheroids and tumor xenograft.

RESULTS: We demonstrated that lipoplatin exhibited a potent antitumoral activity on HeLa, ME-180 cells and its cisplatin-resistant clone R-ME-180. Lipoplatin inhibited cell proliferation in a dose-dependent manner and was more active than the reference drug cisplatin in R-ME-180 cells and induced apoptosis, as evaluated by Annexin-V staining and DNA fragmentation, caspases 9 and 3 activation, Bcl-2, and Bcl-xL down-regulation, but Bax up-regulation inhibited thioredoxin reductase (TrxR) enzymatic activity and increased reactive oxygen species (ROS) accumulation; reduced EGFR expression and inhibited both migration and invasion. R-ME-180, but not ME-180 cells, generated three-dimensional (3D)-multicellular spheroids expressing the cancer stem cell marker ALDH. The ability of R-ME-180 cells to form spheroids in vitro and tumors in nude mice was also remarkably decreased by lipoplatin.

CONCLUSIONS: Overall, our results suggest that lipoplatin has potential for the treatment of cisplatin-resistant cervical cancer.

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RESEARCH ARTICLE

Effect of cisplatin containing liposomes formulated by unsaturated chain-containing lipids on gynecological tumor cells

Paola Ringhieri[1], Alessandra Pannunzio[2], Angelina Boccarelli[2], Giancarlo Morelli[1,2], Mauro Coluccia[3], and Diego Tesauro[1,2]

[1]Department of Pharmacy and CIRPeB, University of Naples "Federico II", Naples, Italy, [2]Istituto Di Biostrutture E Bioimmagini – CNR, Naples, Italy, and [3]Department of Pharmacy-Drug Sciences, University of Bari "Aldo Moro", Bari, Italy

Abstract

Gynecological tumors are major therapeutic areas of platinum-based anticancer drugs. Here, we report the characterization and *in vitro* biological assays of cisplatin-containing Egg L-α-phosphatidylcholine liposomes with different amounts of cholesterol. Dynamic light scattering estimated sizes of all obtained liposomes in the 100 nm range that are suitable for *in vivo* use. On the basis of these data and of the drug loading values, the best formulation has been selected. Stability and drug release properties of platinum-containing liposomes have been verified in serum. The growth inhibitory effects of both liposomal and free drug in a panel of ovarian and breast human cancer cell lines, characterized by a different drug sensitivity, give comparable or better results with respect to free cisplatin drug.

Keywords

CDDP, cisplatin, drug delivery, gynecological tumors, liposomes

History

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RESEARCH PAPER

A Study of Liposomal Formulations to Improve the Delivery of Aquated Cisplatin to a Multidrug Resistant Tumor

Yucheng Zhao[1,2,3] · Jonathan P. May[1,2] · I-Wen Chen[2,3] · Elijus Undzys[2] · Shyh-Dar Li[1,2,3]

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ABSTRACT

Purpose This study was aimed at exploring the use of liposomes to deliver aquated cisplatin (ACP), a metabolite of CDDP, with increased potency and toxicity. Three liposomal formulations were compared for delivery of ACP to a multidrug resistant tumor.

Methods Three different liposomes (DMPC, DPPC and DSPC as the main lipid components) were loaded with ACP by the thin-film hydration method. *In vitro* drug release was assessed over 72 h at 37°C in PBS. The pharmacokinetics of free CDDP and the three ACP liposomes was determined using ICP-AES and their efficacy against EMT6-AR1 multidrug resistant murine breast tumor

DPPC and 130-fold for DMPC. The DSPC formulation displayed the highest drug accumulation in the tumor with 2-fold, 3-fold and 100-fold increases compared to DPPC, DMPC and free CDDP respectively. The DSPC formulation significantly inhibited the EMT6-AR1 tumor growth by ~90%, while the other formulations displayed no statistically significant improved activity compared to saline.

Conclusion These results suggest that the DSPC liposomal formulation is a promising formulation for MDR tumor therapy over DMPC and DPPC formulations and free drug.

KEY WORDS aquated cisplatin · cisplatin · long circulating liposome · multidrug resistant tumor

Thank you…