Lipoplatin monotherapy for oncologists

Dr. George Stathopoulos demonstrated that Lipoplatin monotherapy against adenocarcinomas of the lung can have very high efficacy (38% partial response, 43% stable disease) with only minimal (Grade I) toxicity applied as second-line chemotherapy (after failure of the recommended first-line treatment).


It is anticipated that the success of this treatment will be even higher when applied as first line.

A total of 21 patients (2 patients 1st-line, 10 as 2nd-line and 9 as 3rd-line) were treated in this study.

All 21 patients were evaluable for toxicity. Grade 1 myelotoxicity in two (9.52%) patients. Grade 1 nausea and vomiting in 4 (19.05%) patients. Grade 1 fatigue and peripheral neuropathy in 3 (14.29%) patients. No alopecia.

During the time of the drug infusion, temporary myalgia was observed in 5 patients, but it lasted for only 5-10 min.

Notably, no renal toxicity was detected, even after the 6th treatment course.

The monotherapy study shows significant response rate of Lipo/Nanoplatin in NSCLC mostly applied as second- and third-line. A partial response of 38% with 43% SD as second-line chemotherapy is considered significant rarely seen with other drugs.

Because this is the best result in monotherapy among 1,000 FDA-approved drugs Lipoplatin monotherapy can be applied to lung cancer as first-line treatment

Monotherapy with Lipoplatin vs other drugs

<table>
<thead>
<tr>
<th>Lipoplatin in NSCLC (2nd and 3rd-line)</th>
<th>PR 38%</th>
<th>SD 43%</th>
<th>Grade 1 myelotoxicity, 9.5%</th>
<th>Grade 1 nausea and vomiting, 19%</th>
<th>Grade 1 fatigue and peripheral neuropathy, 14%</th>
<th>temporary myalgia, 24%</th>
<th>Renal toxicity, 0%</th>
<th>Neuropathy, 0%</th>
<th>Stathopoulos et al. Oncol Lett. 2012 4:1013-1016. <a href="http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499504/pdf/ol-04-05-1013.pdf">http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499504/pdf/ol-04-05-1013.pdf</a></th>
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<tbody>
<tr>
<td>Cisplatin in NSCLC (1st-line)</td>
<td>PR 11%</td>
<td>median survival 7.6 months; One-year survival 28%;</td>
<td>Grades ½; Nausea and vomiting 21% and 19%; renal 2%; neurotoxicity 8.6%</td>
<td>Sandler et al, 2000 J Clin Oncol 18:122-130.</td>
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### Oxaliplatin in colorectal

| PR 10% as 2nd-line | First-line Grade 3 neuropathy in 13% Grade 3 neutropenia in 5.2% Grade 3 thrombopenia in 7.9% Grade 3/4 vomiting in 7.9% Grade 3 diarrhea in 2.6% | Becouarn and Rougier 1998 Semin Oncol. 25: 23-31. Bécouarn et al 1998 J Clin Oncol. 1998 16: 2739-44. |

### SPI-077 in NSCLC (liposomal cisplatin of SEQUUS/ALZA/J&J)

| PR 4.5% | Grade 1,2 anemia 81% Grade 1,2 nausea 38% Grade 3,4 nausea 7.7% Grade 3 itching 3.8% Grade 1,2 rash 15.3% | White et al, 2006 Br J Cancer 95, 822-828 http://www.nature.com/bjc/journal/v95/n7/full/6603345a.html |

### Avastin in ovarian cancer

| PR 16% | Grade 3 to 4: hypertension (9.1%), proteinuria (15.9%), GI perforations (11.4%), arterial thromboembolic events (6.8%), deaths (6.8%), bleeding (2.3%), wound-healing complications (2.3%) | Cannistra et al, J Clin Oncol. 2007 25:5180-6 |

### Kyprolis (Onyx) for multiple myeloma (Carfilzomib is a modified tetrapeptidyl epoxide)

| PR 18% | Grade 3 and 4 (Serious) adverse reactions: 45%. Fatigue, 56%; Anemia 47%; Nausea, 45%; Thrombocytopenia, 36%; Dyspnea, 35%; Diarrhea 33%; Pneumonia, 10%; Acute renal failure, 4%; Congestive heart failure, 3% | Zangari et al 2011 Eur J Haematol. 86:484-7. |

Cisplatin monotherapy induces to patients much higher toxicities (Grade 3, 4) compared to 0% Grade 3, 4 after Lipoplatin treatment. In addition, cisplatin displays a much lower efficacy than Lipoplatin in monotherapy studies (11.1% for cisplatin vs 38.1% for Lipoplatin). These facts are summarized in the Table that follows. Cisplatin is considered to be the best drug or the “Queen of Chemotherapy” among approximately 1,000 oncology products approved by FDA and EMA. Cisplatin has also a very broad spectrum against the vast majority of human cancers of epithelial origin (About 80-90% of cancers are epithelial malignancies). The fact that Lipoplatin displays such a big difference in efficacy compared to cisplatin advocates for the value of this drug in cancer management.

<table>
<thead>
<tr>
<th>Toxicities and response</th>
<th>Cisplatin monotherapy</th>
<th>Lipoplatin monotherapy</th>
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<tbody>
<tr>
<td>Grades 3/4 hematologic toxicities</td>
<td>0.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Grades 3/4 Neutropenia and thrombocytopenia</td>
<td>4.5% and 3.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Grades 3/4 Anemia (low hematocrit)</td>
<td>6.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Grades 3/4 febrile neutropenia</td>
<td>0.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Grades 3/4 Nausea and</td>
<td>21% and 19%</td>
<td>0%</td>
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vomiting
Grades 3/4 renal toxicity  2%  0%
Grades 3/4 Neurotoxicity  8.6%  0%

Overall response rate  11.1%  38.1%

References


Lipoplatin Monotherapy with low-dose radiation
Clinical studies pioneered by Professor Koukourakis at the University Hospital of Alexandroupolis using fractions of radiation therapy (RT) in combination with Lipoplatin against gastric cancer patients have shown up to 80% complete response. Details of the study: Patients with locally advanced gastric cancer. Lipoplatin weekly 120 mg/m² (D1). 5-FU weekly 400 mg/m² (D1). Radiotherapy at 3.5-Gy fractions on D2,3,4. 4 of 5 patients had complete response after 5 weekly cycles (Koukourakis et al, 2010 Int J Radiation Oncology Biol Phys 78, 150-155). This was the first clinical demonstration of a very high efficacy of the combination of Lipoplatin + RT. Although the study included 12 patients it is hoped to stimulate oncologists to apply this treatment in larger trials. A similar study by the same group has been extended to NSCLC using Lipoplatin monotherapy + RT with excellent efficacy and low toxicity.

A Ph.D. Thesis in Canada has shown that Lipoplatin has the best synergistic effect with radiation therapy in cell culture or in animals against glioblastomas (brain tumors) compared to other platinum drugs (cisplatin, oxaliplatin, carboplatin). The explanation is that Lipoplatin increases the intracellular uptake of the drug and the damage to the cell is much higher; then concomitant treatment with radiation enhances the damage to the point where the cancer cell is unable to repair and commits apoptotic death.

Application of Lipoplatin on Day 1 and Day 2 on cancer patients (to divide the dose and avoid side effects) and its combination with low-dose radiation therapy (2 Gy on Day 2) enhances 14 times the radiosensitizing potential of Lipoplatin as shown in preclinical studies in Canada. In these studies, Lipoplatin™ and other platinum drugs were tested on the F98 glioma cells for their ability to improve the cell uptake and increase the synergic effect when combined with ionizing radiation. Lipoplatin was shown to have the best radiosensitizing potential among all platinum compounds on F98 glioma cells. After 4 h exposure with platinum compounds, cells were irradiated (1.5 to 6.6 Gy) with a 60Co source. Lipoplatin compared to cisplatin improved the cell uptake by 3-fold because of its liposomal nature, and its radiosensitizing potential was enhanced by 14-fold (Charest et al, 2010).

Charest et al (2010) Concomitant treatment of F98 glioma cells with new liposomal platinum...
When a similar protocol is being applied to human cancer patients the efficacy of Lipoplatin is expected to increase by a factor of 14 by combining with low-dose radiation. Thus, the new treatment protocol is providing to the medical community a drug many times more efficacious than the queen of chemotherapy, cisplatin, and without side effects. This is bringing a true revolution in cancer treatment.

Lipoplatin could become the drug of choice for all three major human cancers (lung, breast, prostate) but also in a number of smaller cancer indications. Furthermore, because of low toxicity could find application against pediatric tumors. Its liposomal nature enhances penetration through the blood-brain barrier for brain and spinal cord tumors whereas targeting of the bone marrow by liposomes makes our drug an excellent candidate for childhood and adult leukemias.

In the image below, a 95% tumor reduction of a high-grade osteosarcoma was obtained when the patient was treated with dose-intense Lipoplatin monotherapy and fractionated radiation over a 25-week period. The patient had failed first and second-line chemotherapy. Our treatment was void of toxicities.

The images show PET/CT scans before (left) and after (right) Lipoplatin - radiation therapy in a patient with high-grade osteosarcoma. A significant lower metabolic activity of the mass can be seen consistent with approximately 95% response. Osteosarcoma, a bone cancer most commonly seen in adolescents and young adults, is usually a high-grade malignancy treated with four “old” drugs, namely methotrexate, doxorubicin (Adriamycin), cisplatin, and ifosfamide that cause severe side effects. Unfortunately, the past 30 years have witnessed few, if any, survival improvements. Our treatment offers a new regiment against osteosarcomas without side effects and an amazing efficacy.

Thus, when combined with external radiation to the tumors where the nanoparticles with their toxic payload have accumulated, the result is a much better efficacy unlike any other regimens in clinical practice. With this treatment, Lipoplatin monotherapy and low-dose radiation achieve spectacular results in the management of terminal cancer patients.

Other case reports where Lipoplatin and low-dose radiation were combined include:

- **Osteosarcoma on a 19-year old patient. Result: Complete cure** without side effects.
- **Kidney cancer stage 4.** Application of this method resulted in complete cure of the patient without side effects.
**Breast cancer** stage 4 with multiple metastases to the chest bones: Partial response and increase in Quality Of Life without side effects from the treatments.

**Non-small cell lung cancer** stage 4. Partial response and increase in Quality Of Life without side effects from the treatments.

**Prostate cancer** stage 4 hormone-independent with bone metastases. Partial response. The pain from bone metastases was gone after the second Lipoplatin infusion. Increase in Quality Of Life. Continuous drop in PSA as a marker.

**Cervical cancer**, stage 4. Partial response and increase in Quality Of Life without side effects from the treatments.

**Glioblastoma**, 6.8 cm in size. Partial response and increase in Quality Of Life. The patient had a life expectancy of few weeks but lived for 2 years and passed away from a complication unrelated to treatment.

**Leukemia**, severe case, 82-year patient. Amazing reduction in blasts from 180,000 to 4,000 without affecting the “good” white and red blood cells. Increase in Quality Of Life without side effects from the treatments.

**Global regimen with no limits**
Lung cancer is the leading cancer in eastern Europe and Asia in males whereas prostate cancer in countries where people smoke less (USA, Western Europe, Australia) the leading cancer is prostate cancer.
In Females breast cancer is the predominant form of cancer except China (lung), Mongolia (liver because of hepatitis virus), India and some African regions (cervix of the uterus because of Human Papilloma Virus).

Lipoplatin could become the drug of choice for all three major human cancers (lung, breast, prostate) but also in a number of smaller cancer indications. Furthermore, because of its low toxicity, our treatment could find application against pediatric tumors. Its liposomal nature enhances penetration through the blood-brain barrier for brain and spinal cord tumors whereas targeting of the bone marrow by liposomes makes our drug an excellent candidate for childhood and adult leukemias.