

Accelerated Radiation Therapy using Altered Fractionation Combined with Chemotherapy in Stage III Inoperable Non-Small Cell Lung Cancer: An Analysis Of Two Prospective Phase II Trials

Munther Ajlouni, M.D*., Robert Chapman, M.D**., Samir H. Patel, M.D*., Mei Lu, Ph.D***., Benjamin Movsas, M.D*.,
Jae Ho Kim, M.D. Ph.D.*

Henry Ford Health System,
Departments of Radiation Oncology*,
Hematology/Oncology** and Biostatistics***

Partially supported by a grant from GlaxoSmithKline

Background

- The average rate of grade 3/4 esophagitis with standard concurrent RT/Chemo is about 25-30%
- The average rate of pneumonitis with standard concurrent RT/Chemo is about 10-15%
- 5 year overall survival rates with standard concurrent RT/Chemo is approximately 15%
- Two phase II trials were conducted in an attempt to reduce treatment related toxicity and improve survival

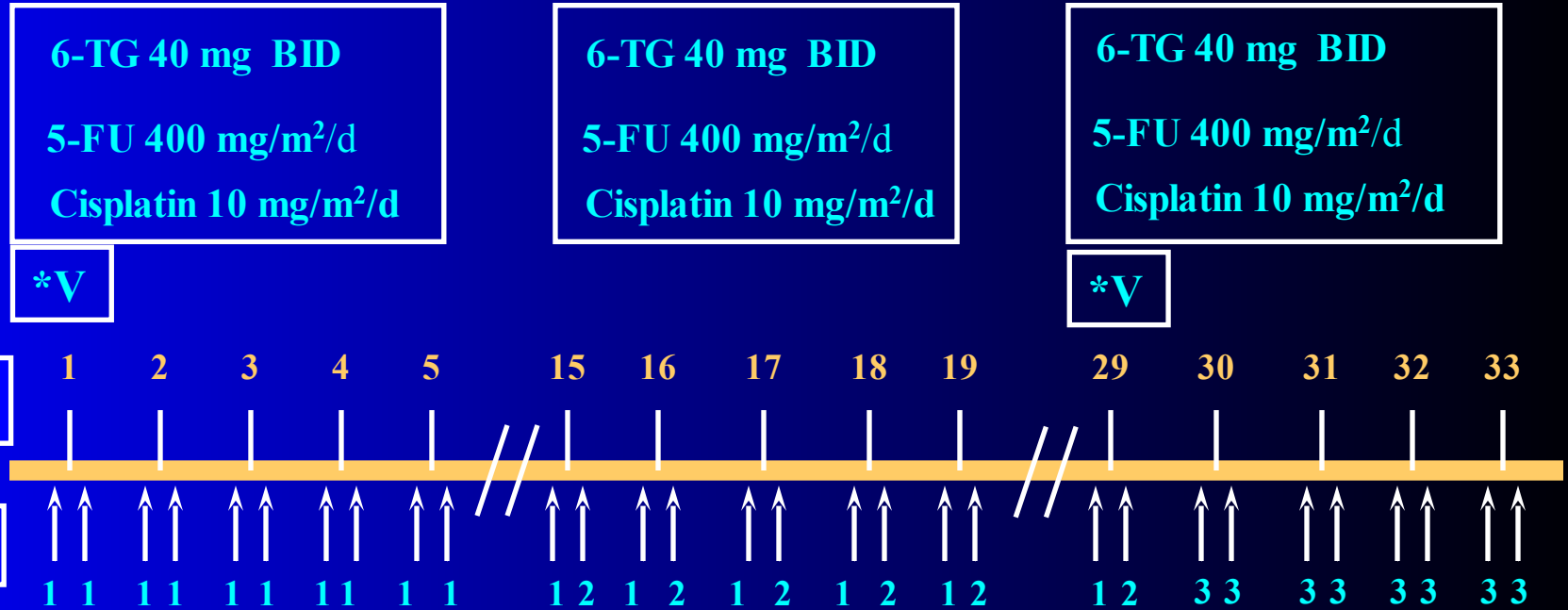
Rational for the First Phase II Trial

- Altered fractionation was utilized in order to reduce the overall treatment time while reducing toxicity
- Data was available demonstrating significant radiation enhancement with 6-thioguanine in an animal model.¹
- 5-Fluorouracil and Cisplatin were commonly used as radiation enhancers at the time the trial was conducted
- Vinblastine was commonly used for the treatment of non-small cell lung cancer at the time the trial was conducted

¹Kim JH, Alferi AA, Kim SH, Hong SH: Radiosensitization of two murine fibrosarcomas with 6-thioguanine. *Int j Radiat Oncol Biol Phys* 1990;18:583-586.

Treatment Schema - Lung Study I

September 1990 - February 1993



RT 1 = Radiotherapy: AP - PA fields to the target volume, 1.8 Gy per fraction
 RT 2 = Radiotherapy: Off- cord fields to the target volume, 1.8 Gy per fraction
 RT 3 = Radiotherapy: Boost field to the tumor volume, 2.0 Gy per fraction
Total RT Dose = 55.60 Gy

*Vinblastine 4mg/m² by IV push

Post-RT Chemotherapy
 CISPLATIN (120 mg/m²) days 1 & 29
 VINBLASTINE (4 mg/m²) days 1, 2, 15, 6,29&30

Rational for the Second Phase II Trial

- Altered fractionation was utilized in order to reduce the overall treatment time while reducing toxicity
- Interrupted accelerated RT was found to be very well tolerated in the first trial allowing for dose escalation¹
- Carboplatin and Vinorelbine are active agents in the treatment of non-small cell carcinoma
- Topotecan was felt to be a significant radiation enhancer²

1. Ajlouni M, Chapman R, Kim JH: Accelerated-Interrupted radiation therapy given concurrently with chemotherapy for locally advanced non-small cell lung cancer. *The Cancer Journal from Scientific American*. 1996;2(6):314-320.

2. Jae Ho Kim, M.D., Ph.D., Sang Hie Kim, Ph.D., Andrew Kolozyvary, B.S. And Mark S. Khil, M.D.: Potentiation of radiation response in human carcinoma cells in vitro and murine fibrosarcoma in vivo by topotecan, an inhibitor of DNA topoisomerase I. *Int J Radiat Oncol Biol Phys*. 1992;22(3):515-8.

Preclinical Study of Topotecan as Radiation Sensitizer (Meth-A induced Fibrosarcoma in Mice)

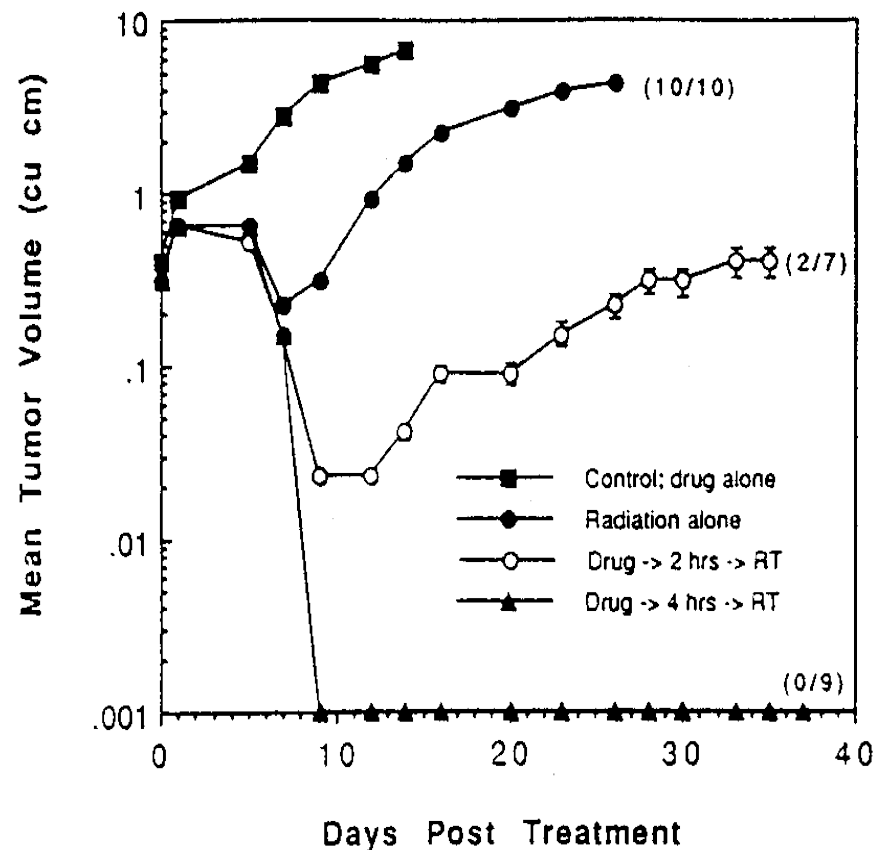


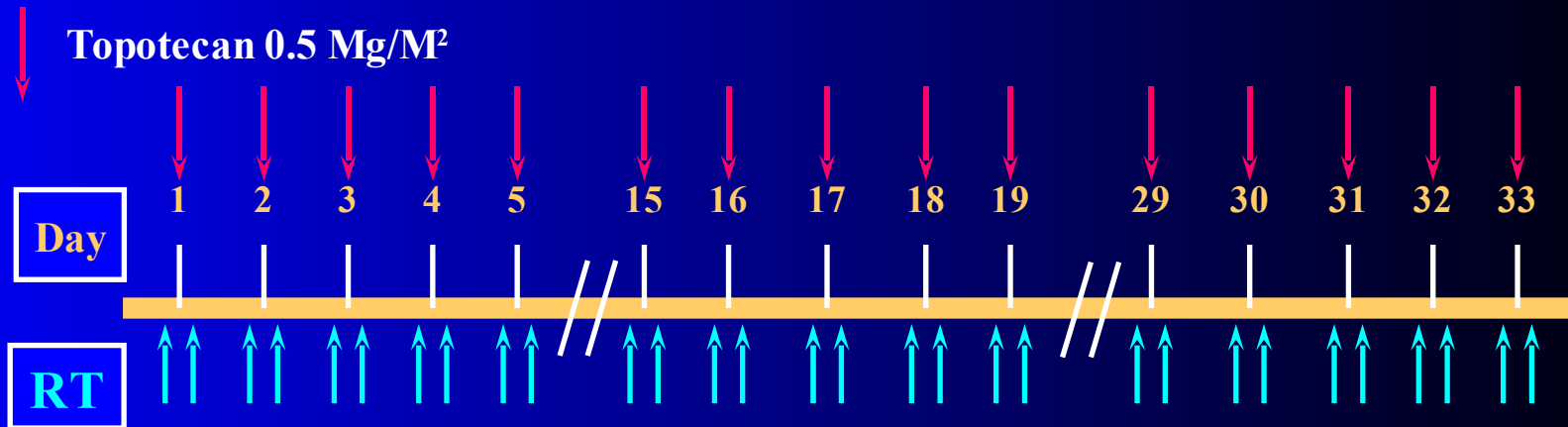
Fig. 4. Tumor growth delay of Meth-A fibrosarcoma after a single dose of radiation (25 Gy). A single dose of topotecan (20 mg/kg) was administered to mice at 2 hr and 4 hr before irradiation. The numbers in parentheses refer to recurrences. Error bars indicate SEM.

Treatment Schema - Lung Study II

June 1999 - December 2003

Pre-RT Chemotherapy

Carboplatin 5.5 AUC on Days 1 & 22
Vinorelbine 25 mg/M² on Days 1, 8, 22 & 29



RT: 3D Treatment Planning Total RT Dose = 60.0 Gy at 2.0 Gy per fraction

PTV = GTV +1.5 cm

Adjacent borderline enlarged nodes included in GTV

Eligibility Criteria for Both Trials

- **Histologically or cytologically proven non-small cell lung cancer. Carcinoids are excluded.**
- **Patients must have had unresectable Stage IIIA or IIIB disease**
- **No evidence of extrathoracic metastases**
- **24 hour creatinine clearance of 60 ml/min or greater. White blood count equal to 4000, platelet count greater than 100,000.**
- **Patients previously treated with radiation or chemotherapy were ineligible**
- **Patients with a prior diagnosis of a second malignancy except for basal cell carcinoma of the skin were ineligible**
- **Patients with symptomatic congestive heart failure were ineligible**
- **All patients must have been capable of and willing to sign an IRB approved consent form**
- **Patients had to be older than 18 years of age**
- **Patients had to have a Karnofsky performance score of at least 60**

Patient Accrual

- Trial I: 35 patients accrued
- Trial II: 37 patients were accrued, 35 patients were evaluable
- Total evaluable patients: 70

RESPONSE

Response	Trial I	Trial II
CR	4	5
PR	18	20
SD	11	6
PD		4
NE	2	
Total Response	22 (63%)	25(71%)

CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, NE: Not Evaluable

Survival

	Trial I	Trial II
Med. F/U	78.3 mo	17.4 mo
Med. Survival	17.2 mo	18 mo
1 Year Survival	69%	62%
2 Year Survival	37%	41%
3 Year Survival	20%	33%
5 Year Survival	17%	

Grade 3/4 Toxicity

	Trial I	Trial II	Trials I & II
Esophagitis (Grade 3/4)	1 (3%)	0	1 (1.5%)
Esophagitis (Grade 2)	6 (17%)	6 (17%)	12 (17%)
Radiation Pneumonitis	2 (6%)	2 (6%)	4 (6%)
Anemia	7 (20%)	17 (49%)	24 (34%)
Leukopenia	24 (69%)	27 (77%)	51 (73%)
Thrombocytopenia	2 (6%)	2 (6%)	5 (6%)

Summary

- Accelerated radiation therapy (ART) as utilized in these 2 trials appears feasible and well tolerated
- The rate of radiation esophagitis is very low as compared with standard radiation/chemotherapy regimens
- The overall time of treatment is reduced using this regimen
- Response rates, median and 3 year survival rates are favorable and comparable with other RT/chemo regimens used for unresectable non-small cell carcinoma of the lung
- Due to the very low rates of radiation related toxicity and the advent of more sophisticated RT techniques, increased intensification of the ART with chemotherapy should be investigated to further enhance the therapeutic ratio

References

1. Kim JH, Alfieri AA, Kim SH, Hong SH: Radiosensitization of two murine fibrosarcomas with 6-thioguanine. *Int j Radiat Oncol Biol Phys* 1990;18:583-586.
2. Ajlouni M, Chapman R, Kim JH: Accelerated-Interrupted radiation therapy given concurrently with chemotherapy for locally advanced non-small cell lung cancer. *The Cancer Journal from Scientific American*. 1996;2(6):314-320.
3. Wozniak AJ, Crowley JJ, Balcerzak SP., et.al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study *Journal of Clinical Oncology*. 1998;16(7):2459-65
4. Jae Ho Kim, M.D., Ph.D., Sang Hie Kim, Ph.D., Andrew Kolozsvary, B.S. And Mark S. Khil, M.D.: Potentiation of radiation response in human carcinoma cells in vitro and murine fibrosarcoma in vivo by topotecan, an inhibitor of DNA topoisomerase I. *Int J Radiat Oncol Biol Phys*. 1992;22(3):515-8.