

Prolonged metronomic chemotherapy in advanced non-small cell lung cancer patients is associated with long term survival

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Abstract

Metronomic chemotherapy is defined as lower dose and more frequent chemotherapy treatments. Here we report 14 consecutive patients with advanced NSCLC (3 stage IIIB, 11 stage IV) who were treated between 2002 and current time with continuous weekly chemotherapy until disease progression or 6 to 12 weeks beyond optimal response. Patients with disease progression were treated with a salvage weekly chemotherapy regimen until progression. Since 2005, patients who had optimal response were placed on maintenance Tarceva. All patients had ECOG performance status of 0 to 2, initiated 1st line treatment at our clinic and received at least 12 weeks of planned chemotherapy. Results: all patients had either a partial or complete response as their best response during the course of treatment. Even though most patients' responses started to occur after 12 weeks of chemotherapy, some patients experienced continuous improvement of their responses as they continued the low-dose weekly chemotherapy. Median survival of this group of patients was over 36 months. One patient (LF) with bronchoalveolar lung cancer had a partial response in her lungs but developed brain metastasis that progressed soon after whole brain radiation therapy. She was then placed on Tarceva and survived for 13 months. Another patient (JM) died of possible stroke while still in PR. Overall chemotherapy-related side effects from treatments were mild. Conclusion: metronomic chemotherapy may be associated with long term survival in patients with advanced non-small cell lung cancer. Further clinical trials to confirm these findings are warranted.

Background

Chemotherapy can prolong the survival and improve the quality of life in patients with advanced non-small cell lung cancer(NSCLC). However, conventional chemotherapy delivered Q 3-weekly generally induces a response in only 20% of patient and leads to median survival of about 8 to 10 months in patients with metastatic disease(1). It's been debated whether maintenance chemotherapy or sequential administration of chemotherapy before disease progression may improve the treatment outcome of these patients(2). Metaanalysis of previous studies on the duration of chemotherapy in NSCLC found that increasing the duration of chemotherapy may significantly increase the disease-free survival but has also been associated with increasing side-effects of the chemotherapy and did not result in a better overall survival of the patients(3). Metronomic chemotherapy defined as lower dose more frequent chemotherapy may be associated with lower rate of chemotherapy related side effects due to the gentler dosing of chemotherapy agents and may have different biological effects on cancer growth, such as the anti-angiogenesis effect(4), as compared to the conventional chemotherapy and therefore may lead to a better therapeutic outcome (5,6). We report here the characteristics and survival of 14 patients with advanced NSCLC who were treated with prolonged metronomic chemotherapy.

Methods

Retrospective analysis of patients with stage IIIB or IV NSCLC, who initiated 1st line chemotherapy with metronomic dosing at SCTWC between 2002 to current were performed. Patients who had already received more than 2 cycles of conventional Q 3-weekly dosing chemotherapy before starting metronomic chemotherapy were excluded. All patients had ECOG performance status of 0 to 2. First line treatment usually consists of weekly administration of Taxel 70 mg /m² and Carboplatin AUC 2 with or without Avastin. Second line chemotherapy usually consists of weekly administration of taxotere, gemcitabine, navelbine, or almita in different combinations. Treatment decision making was done according the algorithm shown at top right.

Metronomic chemotherapy algorithm for advanced NSCLC

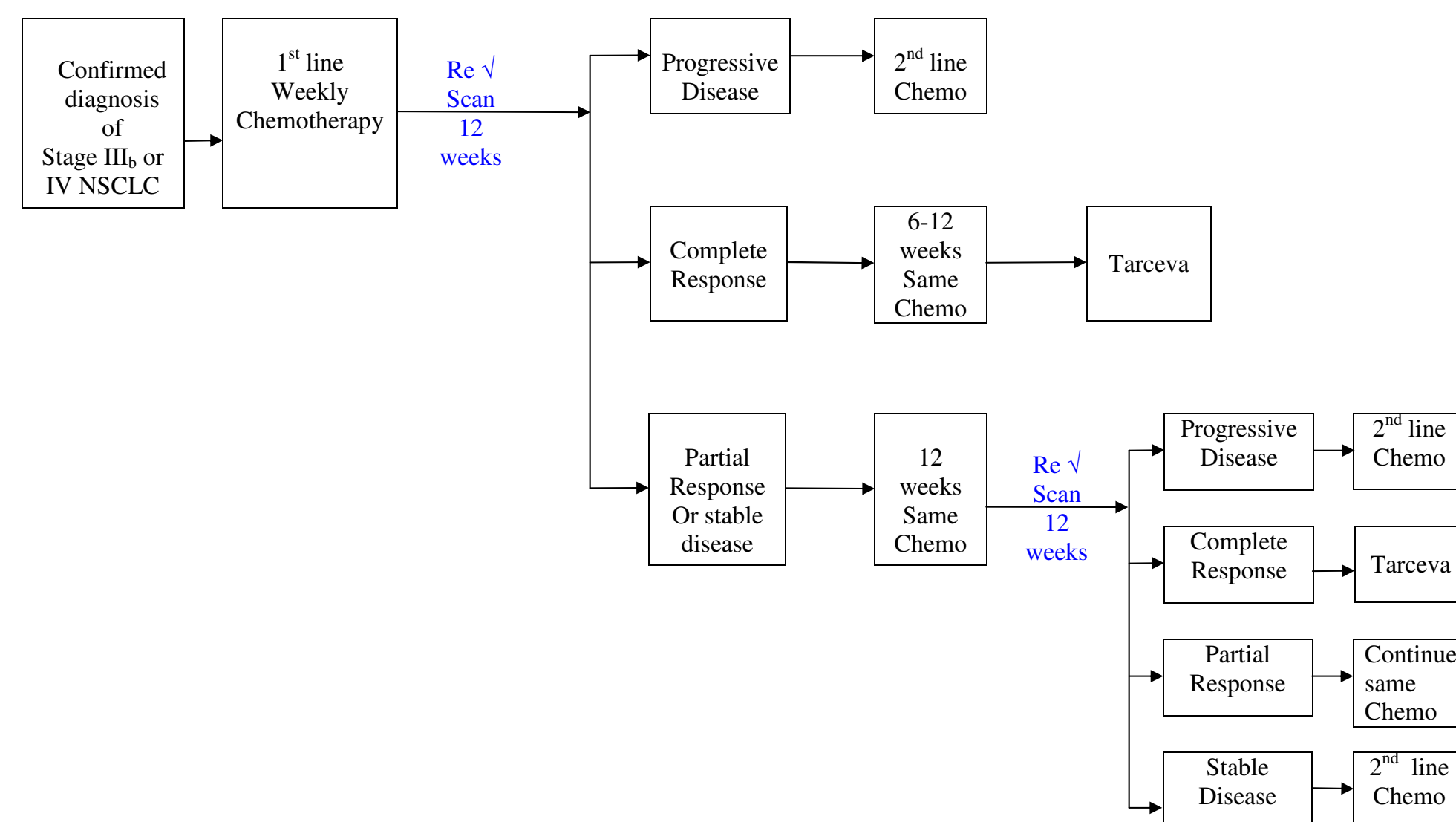


Table 1. Summary of patient information and treatment results

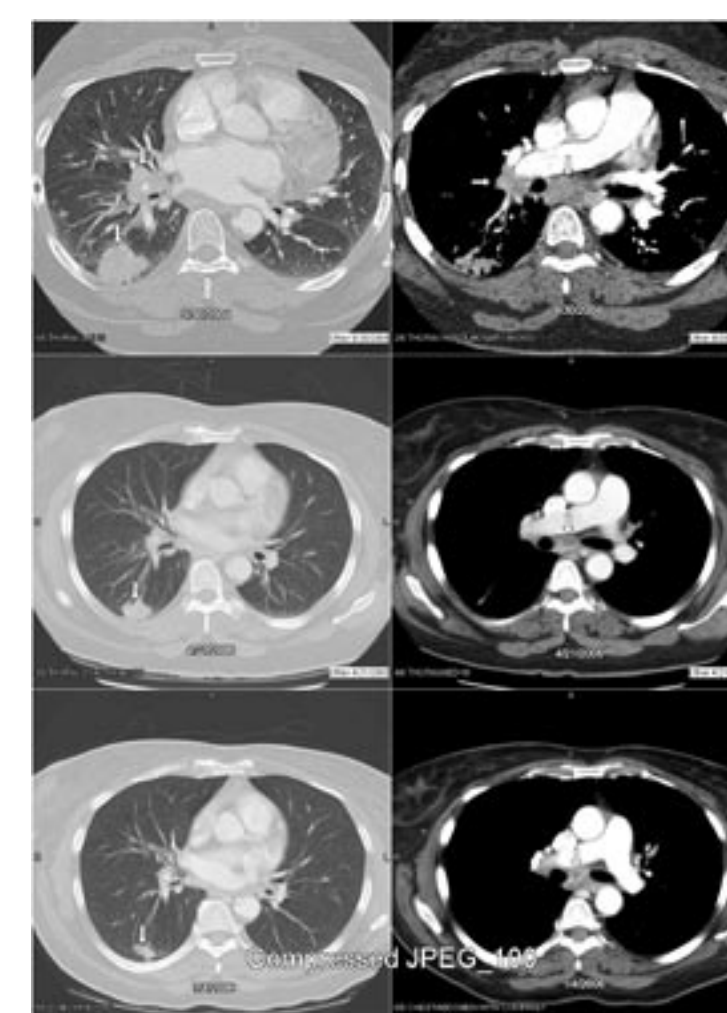
Patient	Age	Sex	Race	Smoking history	Stage/ tissue type	Regimen (1 st line)	Treatment duration (weeks)	Best response	Survival months/ (cause of death)
DM	58	M	W	S	IV /Adeno	TC	66	PR	60 (brain mets)
EC	75	F	A	NS	IV /Adeno	TCFL	35	CR	65+
TK	51	M	W	S	IIIB/Adeno	XRT TC	20	CR	68+
DP	67	F	W	S	IV/Adeno	TC	28	PR	43+
GS	67	M	W	S	IV/squamous	TCFL	24	PR	43+
AT	67	F	AA	S	IIIB/Adeno	TCFL	40	CR	42+
JH	55	M	W	NS	IV/Adeno	TCA	18	nCR	38 (progression)
JC	59	F	W	S	IIIB/Adeno	TC	36	PR	36 (COPD)
BS	64	F	W	S	IV/Adeno	TC	84	PR	26 (infection)
EL	74	F	W	NS	IV/Adeno	TCA	15	CR	16+
MS	47	F	W	S	IIIB/Adeno	TCA	20	CR	15+
RT	46	M	W	S	IV/Adeno	TCA	18	CR	15+
JM	33	M	W	NS	IV/Adeno	TCA	21	PR	11 (Stroke)
LF	78	F	W	NS	IV/BAC	TC	12	PR	13 (brain mets)

Abbreviations: M male, F female, W White, A Asian, AA African American, S Smoker, NS Non-smoker, Adeno Adenocarcinoma, Squamous squamous cell carcinoma, BAC bronchoalveolar carcinoma, TC taxol and carboplatinum, TCFL taxol carboplatinum 5-FU and Leucovorin, TCA taxol carboplatinum and avastin. PR partial response, CR complete response.

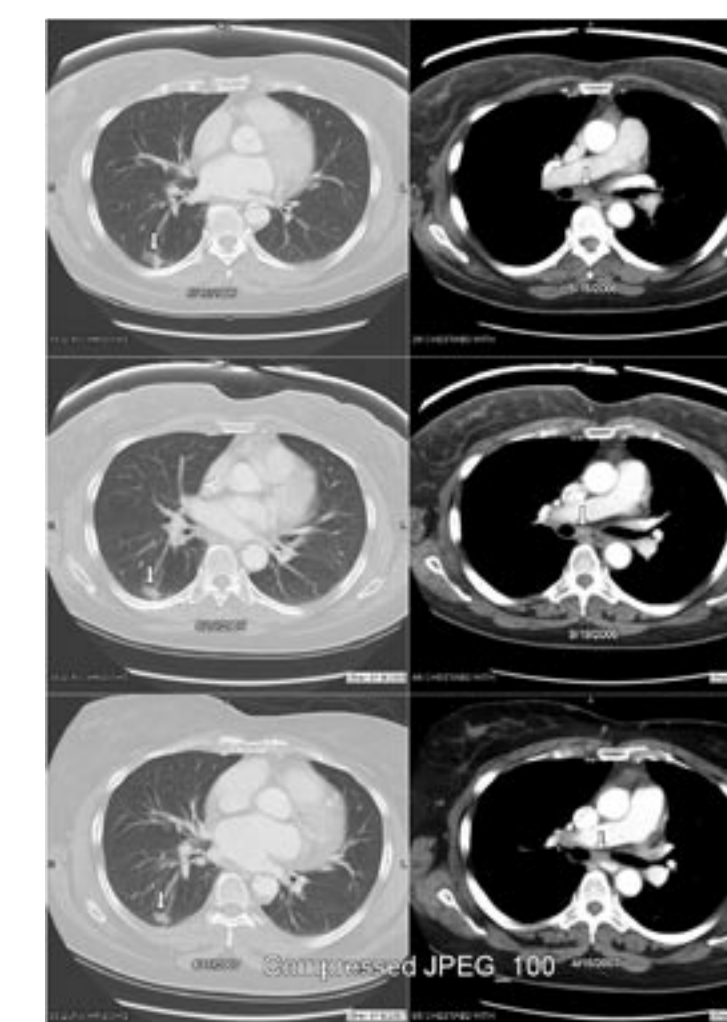
Consecutive radiographic images demonstrating responses during the chemotherapy treatments from typical individual patients



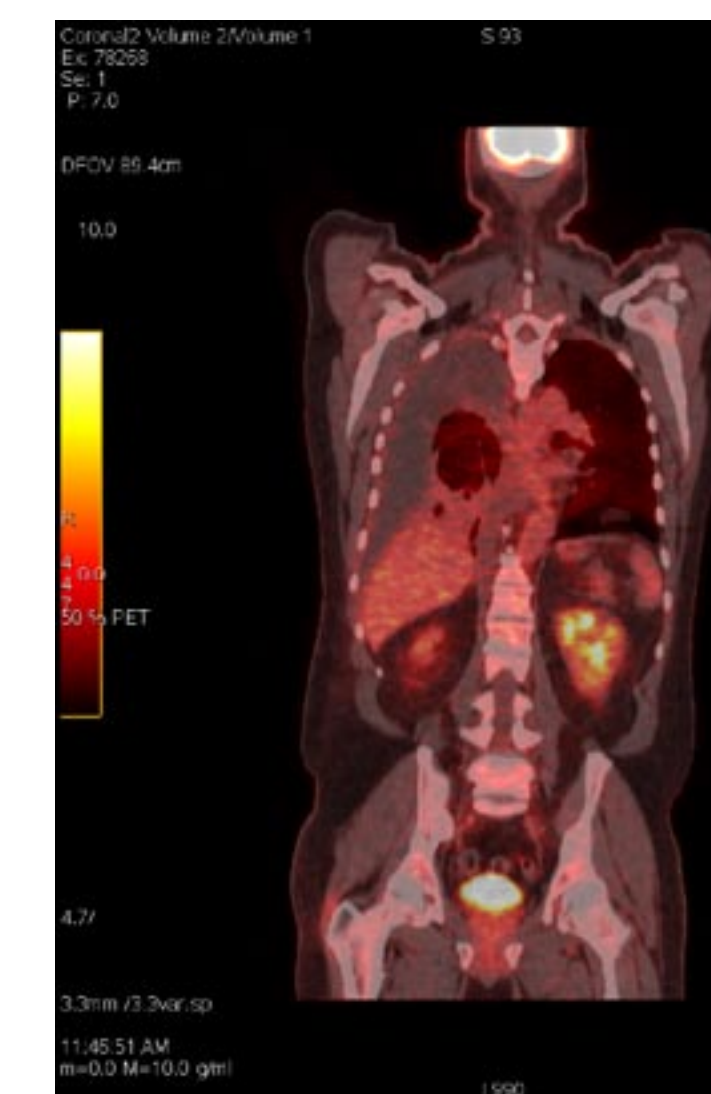
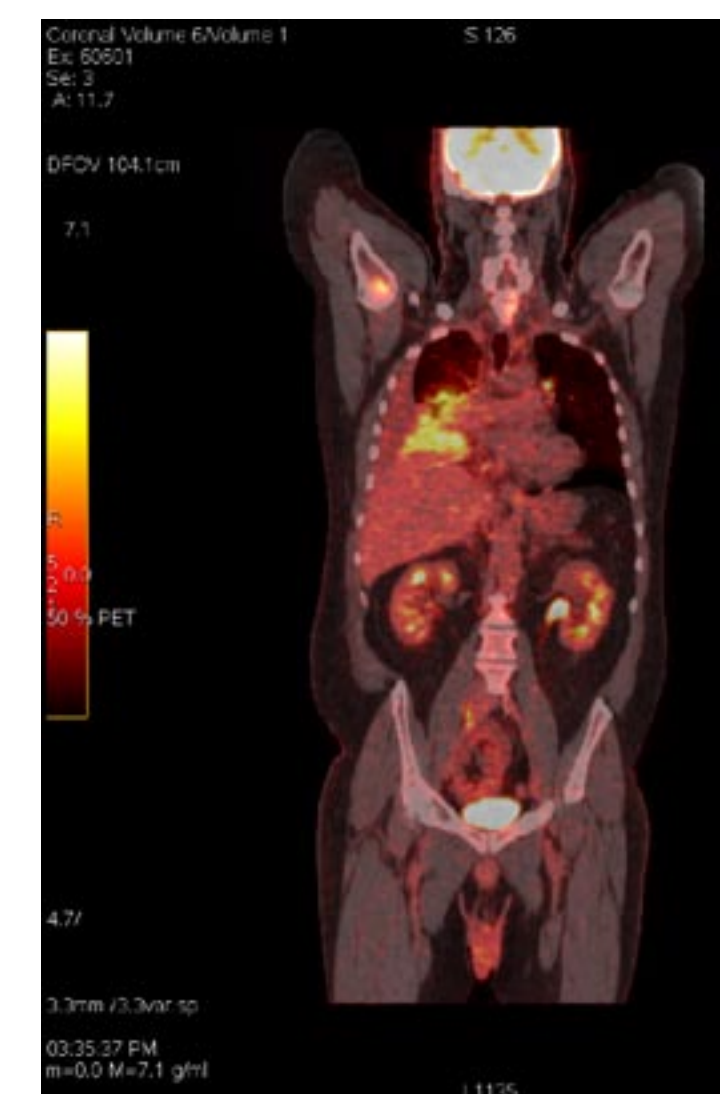
1.EC: From top to bottom, the PET image series at far left depicts the continuous improvement of the stage IV lung cancer from before the chemotherapy (top), to 6 months after the chemotherapy (middle) to 12 months after the chemotherapy (bottom).
2.EC: The image at near left depicts further improvement over time to complete resolution of all residual disease following patient being placed on maintenance Tarceva.



1.AT: From top to bottom, the CT image series at left depict the continuous improvement of the stage IIIB lung cancer before the chemotherapy (top) to 6 months after the chemotherapy (middle) to more than 12 months after the chemotherapy (bottom).



2.AT: Further improvement to near Complete resolution of all residual disease following patient being placed on maintenance Tarceva.



The PET-CT images at left depict the response of progressive stage IV lung cancer to second line chemotherapy.
1.JH (at far left): Before 2nd line chemotherapy.
2.JH (at near left): After 6-months of 2nd line chemotherapy.

Adverse Events

Fatigue: grade 1 10 (70%), grade 2 3 (21%) grade 3 1 (7%)
Peripheral Neuropathy: grade 1 10 (70), grade 2 4(28%)
Neutropenia: grade 1-2 10(70), grade 3 4(28%)
Thrombocytopenia: grade 1-2 6 (43%), grade 3 5 (36%)
Anemia: grade 1 8 (57%), grade 2 4(28%)
Nausea: grade 1-2 9 (64%) grade 3 1(7%)
Diarrhea: grade 1-2 3(21%); grade 3-4 1(7%)
MDS (with 7q13 deletion) 1

Conclusions

1. Prolonged metronomic chemotherapy is associated with dramatic long-term survival in some patients with advanced NSCLC.
2. Response to metronomic chemotherapy may occur gradually over 3 to 12 months while on continuous treatment, therefore, standard 4 to 6 cycles of q 3weekly chemotherapy may not be the optimal chemotherapy duration for advanced NSCLC patients.
3. Metronomic chemotherapy is generally well tolerated, making it possible to administer the treatment over longer period of time, leading to better response rate.
4. Tarceva may play a role in maintaining long term remission in some patients following initial response to chemotherapy.
5. Future clinical trial on the treatment of advanced NSCLC using the paradigm from this study is warranted.

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