Hindawi Publishing Corporation
Journal of Biomedicine and Biotechnology
Volume 2011, Article ID 185646, 5 pages
doi:10.1155/2011/185646

Research Article

Intermittent Chemotherapy and Erlotinib for Nonsmokers or Light Smokers with Advanced Adenocarcinoma of the Lung: A Phase II Clinical Trial

Matjaz Zwitter,[1,2] Mirjana Rajer,[1] Viljem Kovac,[1] Izidor Kern,[3] Martina Vrankar,[1] and Uros Smrdel[1]

[1] *Institute of Oncology, Zaloska 2, 1000 Ljubljana, Slovenia*
[2] *School of Medicine, University of maribor, Slomskov trg 15, 2000 Maribor, Slovenia*
[3] *University Hospital for Pulmonary and Allergic Diseases, Golnik, Slovenia*

Correspondence should be addressed to Matjaz Zwitter, matjaz.zwitter@guest.arnes.si

Received 31 October 2010; Accepted 21 February 2011

Academic Editor: Tony Mok

Copyright © 2011 Matjaz Zwitter et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Intermittent application of chemotherapy and tyrosine kinase inhibitors may avoid antagonism between the two classes of drugs. This hypothesis was tested in a Phase II clinical trial. *Patients and Methods*. Eligible patients were nonsmokers or light smokers, chemo-naïve, with metastatic adenocarcinoma of the lung. Treatment: 4 to 6 cycles of gemcitabine 1250 mg/m^2 on days 1 and 4, cisplatin 75 mg/m^2 on day 2, and erlotnib 150 mg daily on days 5–15, followed by erlotinib as maintenance. *Results*. 24 patients entered the trial. Four pts had grade 3 toxicity. Complete remission (CR) and partial remission (PR) were seen in 5 pts and 9 pts, respectively (response rate 58%). Median time to progression (TTP) was 13.4 months and median overall survival (OS) was 23 months. When compared to patients with negative or unknown status of EGFR mutations, 8 patients with EGFR gene activating mutations had significantly superior experience: 4 CR and 4 PR, with median TTP 21.5 months and OS 24.2 months ($P < .05$). *Conclusions*. Intermittent schedule with gemcitabine, cisplatin and erlotinib has mild toxicity. For patients who are positive for EGFR gene activating mutations, this treatment offers excellent response rate, time to progression and survival.

1. Introduction

To the surprise and deep disappointment of all involved in the treatment of lung cancer, several large trials did not demonstrate any benefit of tyrosine kinase inhibitors (TKIs) as an addition to chemotherapy [1–3]. Virtually all further clinical research on combinations of TKIs and chemotherapy was then abandoned. Basic and clinical research then focused on mutations of the gene for epidermal growth factor receptor (EGFR) as a predictive factor for response to monotherapy with TKIs and to development of new compounds with broader and/or irreversible inhibition.

The biological basis for the negative experience with combined treatment was never given proper attention. Gefitinib and erlotinib met all three standard criteria for inclusion in a combination with chemotherapy: activity as monotherapy, different mechanism of action, and different toxicity. Why, then, did the combination not work? As explained in a recent editorial [4], we believe that the cells of tumors sensitive to TKIs are pushed into the G-0 phase of the cell cycle and therefore become resistant to cytotoxic drugs. If antagonism between the two classes of drugs is really the biological basis for the aforementioned negative experience, then an optimal combination of TKIs and chemotherapy should be in an intermittent, rather than a continuous schedule.

This brief report presents a single-institution experience on intermittent chemotherapy and TKI in a small series of patients with advanced adenocarcinoma of the lung. Our hypothesis was that intermittent treatment would lead to superior time to progression, when compared to experience

with chemotherapy alone. If confirmed, such a result would be a solid basis for a randomised clinical trial.

2. Patients and Methods

2.1. Inclusion Criteria. Patients eligible for the trial were chemonaïve with microscopically confirmed adenocarcinoma of the lung, had stage III B (wet) or IV according to UICC-TNM classification (6th edition), had smoking history of less than 10 packs in years, had an ECOG performance status 0 or 1, and had adequate parameters of hematological, liver, and renal function to receive cisplatin-based chemotherapy. In the absence of neurological symptoms, patients with brain metastases were eligible and were treated with brain irradiation only in case of intracranial progression. All patients were fully informed and gave written consent to participate in the trial.

2.2. Initial Diagnostics. All patients had their diagnosis confirmed by biopsy or cytology. At the time when the trial was initiated, testing for EGFR mutations was not available.

Within three weeks prior to treatment, the precise extent of the disease was determined by chest X-ray and CT scanning of the chest, upper abdomen, and brain. Since 2008, PET-CT scanning has been available and included in the initial diagnostics and in followup.

2.3. Treatment. The treatment started with four cycles of intermittent chemotherapy and erlotinib according to the following schedule:

day 1: gemcitabine 1250 mg/m^2 in 30-minute infusion,

day 2: cisplatin 75 mg/m^2, with appropriate hydration and antiemetics,

day 4: gemcitabine 1250 mg/m^2 in 30-minute infusion,

days 5–15: erlotinib 150 mg daily p.o.

Cycle was repeated on day 22.

Patients received 4 to 6 cycles of intermittent treatment. The number of cycles depended on tolerance to cisplatin-based chemotherapy and was determined individually. Immediately after the last cycle, patients continued with erlotinib 150 mg/m^2 daily continuously until progression or unacceptable toxicity.

2.4. Monitoring for Response, Time of Progression, and Follow-up. Definition of complete response (CR), partial response (PR), stable disease (SD), and progression followed the RECIST criteria [5].

The first evaluation of response was done during the third cycle of intermittent therapy, with confirmation of response during the fifth cycle. After 4 cycles, patients were seen every second month. Control radiological examinations were repeated every 2 months for chest X-ray, every 4 months for CT, and at 6 and 12 months for PET-CT (only patients who had this examination during their initial diagnostics).

2.5. Posttreatment Analysis of Archived Bioptic Material. In October 2010, all biopsy samples were reviewed, and specimens with more than 10% of tumour tissue were analyzed. Genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue sections using QIAAmp DNA FFPE tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Quantification of extracted DNA was done on Qubit Fluorometer (Invitrogen, Carlsbad, USA). To detect EGFR gene-activating mutations, we used TheraScreen EGFR29 Mutation Kit (DxS Diagnostics, Qiagen, Manchester, UK). All realtime PCR reactions were performed in a 25 μL final volume on ABI 7500 instrument (Applied Biosystems, Carlsbad, USA).

2.6. Endpoints and Statistical Planning. The primary endpoint was time to progression. Secondary endpoints were response rate, toxicity, and overall survival.

After standard chemotherapy for metastatic nonsmall cell carcinoma, the expected TTP is 5 months. The size of this single-arm nonrandomised trial of intermittent therapy was based on the assumption of 9 months as the median time to progression (TTP). To obtain such a result with a confidence interval of 6–12 months, we planned to recruit 40 patients.

2.7. Ethical Considerations. The investigators strictly followed recommendations of the Helsinki Declaration (1964, with later amendments) and of the European Council Convention on Protection of Human Rights in Bio-Medicine, as accepted in Oviedo in 1997. The protocol was approved by the Institutional Review Board (Institute of Oncology, Ljubljana) and by the National Committee for Medical Ethics, Ministry of Health, Republic of Slovenia.

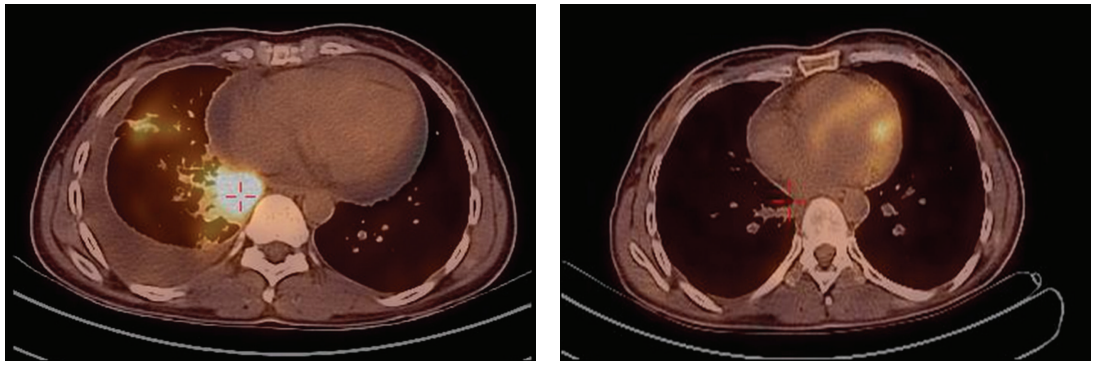
3. Results

3.1. Patient Population. Between September 2005 and July 2010, 25 patients were recruited into the trial. One patient was later found to have metastatic carcinoma of the pancreas rather than primary lung cancer and was excluded from all further analyses.

With 12 patients each, male and female patients were equally represented. Median age was 50 years (range: 25 to 73 years). Twelve patients were never-smokers, and most were in good general condition (PS 0-1 for 21 patients). With the exception of a single patient with "wet" stage III B, all other patients had stage IV disease. Bone metastases were the most common site of metastatic disease, followed by pleura/pericardium, contralateral lung metastases, and liver. Two or more sites of metastatic disease were documented in 4 and 12 patients, respectively (Table 1).

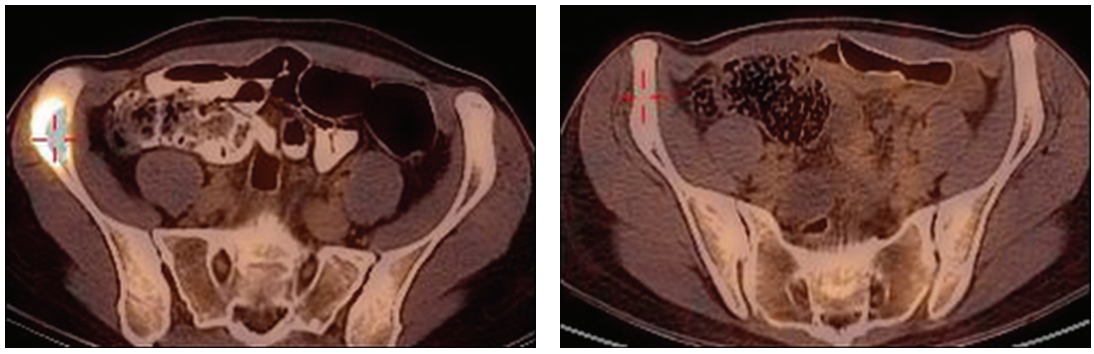
3.2. Analysis of EGFR Mutations in Bioptic Material. Analysis of the archived bioptic material was completed in October 2010.

Three patients had only cytological diagnosis, and an additional 3 had biopsy samples too small to allow for analysis of EGFR mutations in tumor cells. Of the 18 adequate samples, 8 were positive for EGFR gene-activating mutations.



(a) (b)

Figure 1: A woman, 39, never-smoker, developed adenocarcinoma of the right lower lobe, T4 N2 M1b with metastases in bone and liver. 18F-FDG PET-CT before treatment (a) and after 4 months (b). Complete remission was confirmed also a year later.



(a) (b)

Figure 2: The same patient as on Figure 1. Bone metastasis in the right iliac bone (a) and complete response after treatment (b).

3.3. Treatment. The actual number of cycles of intermittent therapy was from 1 to 6 cycles (median: 4 cycles). Due to early progression, one patient did not receive erlotinib as maintenance treatment. In October 2010, 7 patients were still on maintenance treatment with erlotinib, and an additional patient stopped treatment with erlotinib after 12 months in PET-CT confirmed complete remission (Figures 1 and 2). For the remaining patients, median total duration of treatment was 10 months.

3.4. Toxicity. During the initial phase, 3 pts had grade 3 toxicity (2 neutropenia, 1 thrombocytopenia). Side effects of maintenance with erlotinib were skin toxicity (grade 3: 1 pt; grade 2: 11 pts) and diarrhea (grade 2 in 1 pt).

No patient experienced grade 4 or greater toxicity.

3.5. Response to Treatment, Time to Progression, and Survival. All patients are evaluable for response, and no patient has been lost to followup. For the whole group of 24 patients, complete remission (CR) was seen in 5 pts; partial remission (PR) in 9 pts (response rate 58%), minimal response or stable disease (SD) in 8 pts, and progression in 2 pts. A clear and statistically significant ($P < .05$) correlation was seen between the presence of activating EGFR mutations and response. Among the 8 patients who were positive for EGFR gene-activating mutations, 4 complete and 4 partial remissions were seen. On the other hand, no CR and only 2 PR were seen among the 10 patients negative for mutations (Table 2).

For the whole group, median time to progression (TTP) was 13.4 months, and median overall survival (OS) was 23 months. Again, patients positive for EGFR gene-activating mutations had-superior experience. Median TTP and OS for this group was 21.5 months and 24.2 months, respectively. For patients without EGFR mutations, TTP was 5 months, and OS was 7 months (Table 2 and Figures 3 and 4).

4. Discussion and Conclusions

This clinical trial was launched at a time when routine testing for EGFR gene-activating mutations was not yet available. Selection of patients for a combination of chemotherapy and erlotinib was made on the basis of classical histopathology (adenocarcinoma) and smoking status.

Recent developments led to premature closure of our trial. Since testing for EGFR gene mutations is now available,

Table 1: Demographics, prognostic factors, and extent of disease.

	No. of patients
Age	
Median	50
Range	25–73
Gender	
Male	12
Female	12
Smoking	
Never-smoker	12
Light smoker (<10 pack years)	8
Performance status	
EGOG PS 0	5
1	16
2	3
Stage	
III B "wet"	1
IV	23
Site(s) of metastatic disease	
Bone	17
Pleura and pericardium	11
Distant lung	11
Liver and/or suprarenals	10
Distant lymph nodes and/or soft tissues	6
Brain	2
Number of metastatic sites	
1	8
2	4
3 or more	12

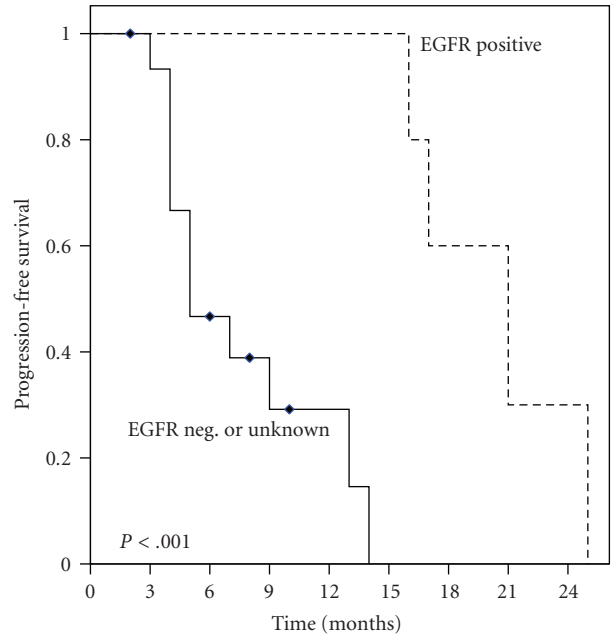


Figure 3: Progression-free survival in relation to the status of EGFR gene activating mutations.

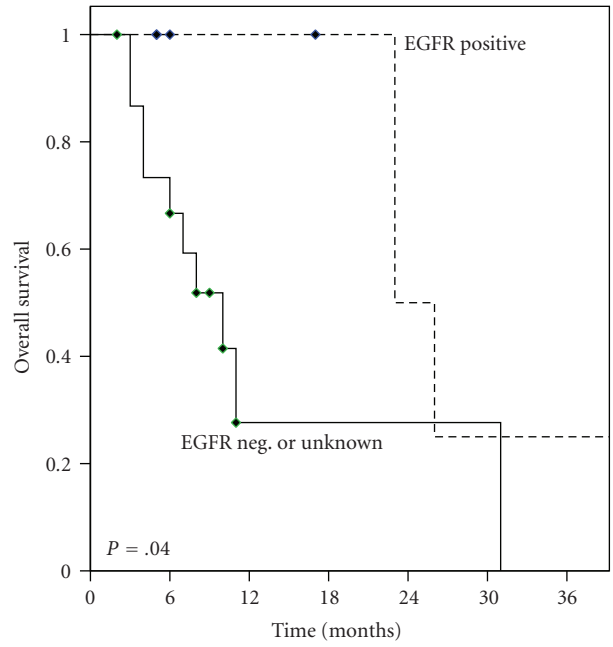


Figure 4: Overall survival in relation to the status of EGFR gene activating mutations

it is clear that patients with activating mutations are those who really benefit from TKIs. In addition, standard first-line treatment for patients with activating EGFR mutations is now monotherapy with a TKI [6, 7]. Since continuing a trial with the same selection criteria and without considering the status of EGFR gene activating mutations was not justified, the research group made a decision to close the trial and analyse the experience.

In order to get a longer interval for intermittent erlotinib, gemcitabine was given on days 1 and 4 of the cycle. When compared to the standard day 1 and day 8 schedule, this minor modification in timing of cytotoxic drugs did not have any adverse effect on the tolerance to treatment. Clearly, other platin-based schedules which apply chemotherapy on a 3-weekly basis (such as pemetrexed-cisplatin or paclitaxel-carboplatin) can offer an even longer interval for TKIs and might be considered for future trials of intermittent treatment.

Two other groups recently reported promising experience with intermittent chemotherapy and TKIs. In a trial from the USA, two schedules of intermittent treatment were tested [6]. In combination with pemetrexed (500 mg/m^2 on day 1), erlotinib was given either as a pulse application in a high dose (range: 800 to 1400 mg) given on days 2, 9 and 16, or in lower doses (150–250 mg daily) on days 2 to 16. Patients had various advanced malignancies, most of which were pretreated. While tolerance to this treatment was good, the small number and heterogeneity of patients recruited into this trial do not allow for any clear conclusion regarding the effectiveness of intermittent treatment. Of more importance is a randomised Phase II trial by Mok

Table 2: Response to treatment, time to progression, and survival in relation to EGFR mutations.

		EGFR mutations			
		Positive	Negative	Unknown	All
Response to treatment	CR	4	—	1	5
	PR	4	2	3	9
	SD	—	6	2	8
	Progression	—	2	—	2
Time to progression (months)	Median (95% CI)	21.5 (14.8–27.2)	5.0 (0.9–9.1)	5.0 (3.9–4.1)	13.4 (5.4–20.6)
Survival (months)	Median (95% CI)	24.2	7.0 (0.1–13.9)	11.0	23.0 (10.9–35.2)

et al. [7]. This study from Asia compared gemcitabine and either cisplatin or carboplatin to a schedule with addition of intermittent application of erlotinib (150 mg on days 14 to 28 of the cycle) and reported significantly superior TTP with the intermittent schedule. Their experience is most valuable but may not be of direct relevance for the rest of the world, due to the well-known differences in sensitivity of lung cancer to TKIs between Asian and Caucasian patients.

Despite its small size, our trial can offer valuable experience for further research on optimisation of treatment with combinations of chemotherapy and TKIs. Looking at the whole series of patients, we can conclude that intermittent chemotherapy and erlotinib is a treatment of very low toxicity. It is also clear that the efficacy of treatment is closely related to the presence or absence of EGFR gene-activating mutations.

The most important finding is the excellent response rate with a substantial proportion of complete responses and prolonged TTP and OS for patients positive for EGFR gene-activating mutations. For many years, the maximal expectation of a patient with metastatic nonsmall cell lung cancer was a partial remission of relatively short duration in the range of 5 to 9 months. With intermittent treatment, we now see durable complete remissions in a subpopulation of patients. While the number of patients in our trial is small and any definitive conclusion would be premature, we nevertheless believe that further research of intermittent therapy for patients positive for EGFR gene-activating mutations is warranted. A randomised trial comparing first-line TKI as monotherapy to the intermittent schedule should clarify the real value of this new approach.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgments

This paper was supported by Grant J3-6044-0302-04 from the Ministry of Science and Higher Education, Republic of Slovenia. The authors thank the nurses from the Outpatient Department and Day Hospital for their valuable help in conducting the trial and Alan McConnell Duff for language editing.

References

[1] G. Giaccone, R. S. Herbst, C. Manegold et al., "Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1," *Journal of Clinical Oncology*, vol. 22, no. 5, pp. 777–784, 2004.

[2] R. S. Herbst, G. Giaccone, J. H. Schiller et al., "Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2," *Journal of Clinical Oncology*, vol. 22, no. 5, pp. 785–794, 2004.

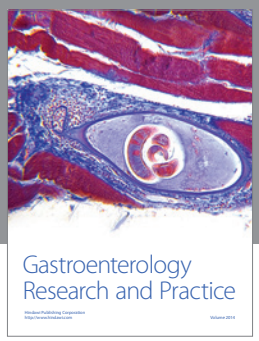
[3] R. S. Herbst, D. Prager, R. Hermann et al., "TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer," *Journal of Clinical Oncology*, vol. 23, no. 25, pp. 5892–5899, 2005.

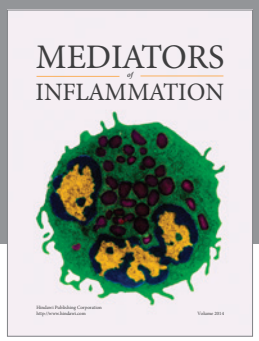
[4] M. Zwitter, "Combining cytotoxic and targeted therapies for lung cancer," *Journal of Thoracic Oncology*, vol. 5, no. 10, pp. 1498–1499, 2010.

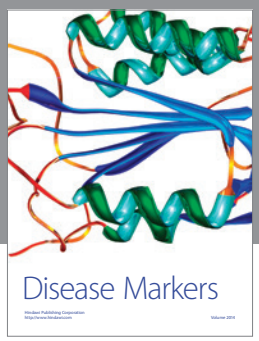
[5] P. Therasse, S. G. Arbuck, E. A. Eisenhauer et al., "New guidelines to evaluate the response to treatment in solid tumors," *Journal of the National Cancer Institute*, vol. 92, no. 3, pp. 205–216, 2000.

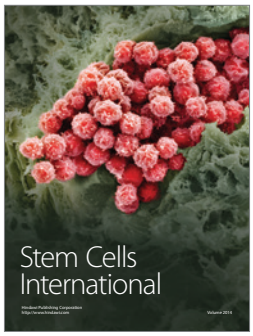
[6] A. M. Davies, C. Ho, L. Beckett et al., "Intermittent erlotinib in combination with pemetrexed : phase I schedules designed to achieve pharmacodynamic separation," *Journal of Thoracic Oncology*, vol. 4, no. 7, pp. 862–868, 2009.

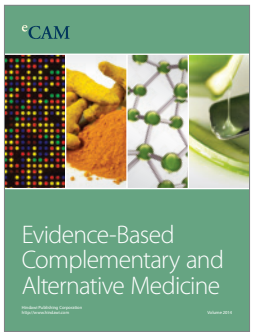
[7] T. S. K. Mok, Y. L. Wu, C. J. Yu et al., "Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer," *Journal of Clinical Oncology*, vol. 27, no. 30, pp. 5080–5087, 2009.

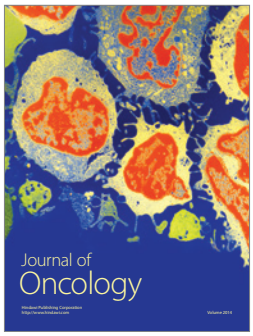


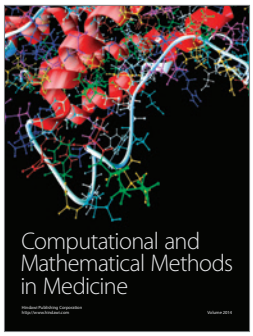


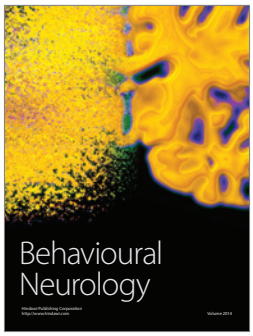


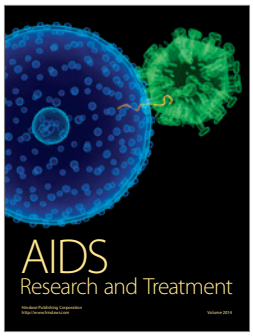


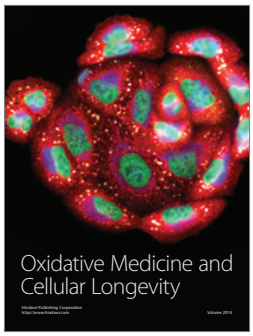












Hindawi

Submit your manuscripts at
http://www.hindawi.com