Gefitinib and Afatinib Treatment in an Advanced Non-small Cell Lung Cancer (NSCLC) Patient Undergoing Hemodialysis

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Abstract. *Renal failure in cancer patients is not a rare clinical condition and often contraindicates anticancer drug treatment; moreover, chemotherapeutic drugs are frequently identified as possible iatrogenic cause of renal failure. Molecular therapies, when appropriate, could represent a therapeutic option for cancer patients with severe renal disease, but the lack of knowledge in this field, at present, limits their use in patients undergoing dialysis. Herein we describe a case, at our knowledge the first reported, of a patient with advanced lung adenocarcinoma on maintenance hemodialysis treated with gefitinib and then with afatinib; we also reviewed the literature on epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) used in NSCLC patients with concomitant renal impairment.*

Renal failure in cancer patients is a frequent clinical condition that often contraindicates the use of chemotherapy, compromising adequate cancer treatment (1, 2). Moreover, chemotherapeutic drugs, in particular platinum derivatives such as cisplatin, are frequently identified as iatrogenic cause of renal failure, configuring renal impairment as a problem of more significant prevalence after first-line of anticancer treatment. When end -stage renal disease is established, chemotherapy is often not feasible and management of anticancer treatments in patients under chronic dialysis is challenging for oncologist and nephrologist (3).

Molecular-targeted therapies, when available, could represent a potential option for cancer patients with end stage renal disease, but the lack of knowledge in this field, at present, limits the widespread use of such drugs in patients undergoing hemodialysis.

Afatinib is an orally-administered irreversible blocker of epidermal growth factor receptor-1 (EGFR/ErbB1) signaling, epidermal growth factor receptor-2 (HER2/ErbB2) and ErbB4; it also inhibits transphosphorylation of HER3. This drug has been recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the first line treatment of advanced NSCLC patients whose tumors harbor activating EGFR gene mutations (4, 5). Indeed, in two multi-center, international, open-label, randomized trials afatinib was shown to prolong progression-free survival with respect to first-line chemotherapy in advanced NSCLC with *EGFR* mutation (6-7). The recommended dose and schedule for afatinib is 40 mg orally once daily until disease progression or severe toxicity. The most frequent adverse reactions are diarrhea, skin toxicity, stomatitis, paronychia and decreased appetite. Serious adverse reactions have been reported in about a third of patients treated with afatinib. Fatal adverse reactions included pulmonary toxicity and sepsis.

No renal failure has been reported during treatment and no data are available on the use of this drug in patients with renal disease of any stage nor in patients undergoing dialysis. Safety, pharmacokinetics and efficacy of afatinib have not yet been evaluated in clinical trials in patients with renal impairment. Despite no initial dosage adjustment is considered necessary in case of mild or moderate renal impairment, treatment with afatinib is not recommended in patients with severely-reduced renal function (creatinine clearance <30 ml/min). Nevertheless, drug excretion primarily occurs through the biliary system, with fecal elimination; less than 5% of a single dose is excreted through the urinary system (8). Herein, we report a case of advanced lung adenocarcinoma on maintenance hemodialysis treated with afatinib.

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Case Report

The patient was a 60-year-old Caucasian woman, never smoker with silent medical history. At the moment of lung cancer diagnosis, in 2004, she was evaluated for persistent dorsal pain; the total body scan showed right pulmonary tumor mass, increased mediastinal lymph nodes and multiple skeletal bone lesions. Transbronchial biopsy of the primary pulmonary mass was consistent with the diagnosis of well differentiated lung adenocarcinoma.

After palliative radiation therapy on collapsed vertebrae, the patient underwent first-line chemotherapy with cisplatin and gemcitabine for three cycles from February, 2004. At the start of this first line treatment, the patients had good performance status (ECOG PS=0), with the subsequent basal blood tests values: WBC=5,38×10^9/l, PLT 279×10^9/l, Hb=11,9 g/dl, Na=140 mEq/l, K=4,3 mEq/l, creatinine=0,8 mg/dl, creatinine clearance=78 ml/min. The treatment was then interrupted despite disease partial response at the CT scan, because of acute development of an hemolytic uremic syndrome (HUS). This is a rare complication of several drugs, including gemcitabine treatment (reported incidence from 0.015% to 2.7% in cases of protracted treatment), characterized by hemolytic anemia, thrombocytopenia, high LDH levels, low haptoglobin level and worsening renal failure (9-13). In our patient, the HUS has been clearly attributed by the nefrologists to gemcitabine, owing to the timing of this drug administration and the initial development of the clinical signs of the syndrome. At the moment of acute HUS development, the patient had WBC=2,23×10^9/l, PLT=75×10^9/l, Hb=7 g/dl, Na=137 mEq/l, K=4,7 mEq/l, creatinine=1,8 mg/dl, clearance creatinine=34 ml/min. Renal impairment became irreversible and the patient was put under cronic dialysis treatment from May 2004.

For the evidence of radiological progression at the bone scan, second-line treatment with gefitinib within a compassionate use program was started in September 2004, with clinical benefit and prolonged response of disease. In August 2010 drug administration was temporarily discontinued due to gastrointestinal toxicity with nausea and diarrhea. Gefitinib was definitely stopped in November 2011, after seven years of treatment with large benefit and lack of complications, for radiological and clinical progression of disease, with the appearance of new bone lesions and mediastinal lymph nodes with dorsal pain. EGFR mutational status of the tumor was not assessed because of lack of adequate histologic specimens, but considering the characteristics of the patient and prolonged benefit with gefitinib, the probability of the presence of an EGFR activating mutation was considered very high. Therefore, the patient was enrolled into a compassionate use program with afatinib (14-16).

At baseline, general conditions were quite good, with minor tumor symptoms (bone pain related to vertebral lesions); renal function was unchanged, with hemodialysis three times per week. The patient started oral treatment with afatinib 30 mg per day, with a primary dose reduction in order to test the tolerability during maintenance hemodialysis, on 14th Nov 2011. Treatment was well-tolerated, with the development of persistent mild asthenia as the only adverse event. Considering good tolerability and clinical benefit, with pain reduction, it was decided on 12th January 2012, after two months of treatment, to increase the dose to 40 mg per day. After a few days, due to the appearance of significant asthenia, vomiting and nausea, she decided by herself to definitively stop drug assumption; no further progression of renal impairment was evidenced due to afatinib treatment and the timing of hemodialysis remained unchanged. On March 2012 a radiological evaluation showed progression of the disease.

Discussion

Molecular therapies and, in particular EGFR-TKIs, represent an important treatment option for a significant proportion of patients affected by advanced NSCLC. Their good tolerability profile and their principal enteric excretion make these drugs an ideal option also for patients with poor PS and major comorbidities, such as end-stage renal failure. A severe renal impairment, although still compatible with relatively long survival, represents an exclusion criterion for enrollment in clinical trials, with consequent lack of available data of new molecular therapies in this clinical situation.

Sharing such clinical cases could be clinically useful, especially in this era in which the available tailored therapies are becoming more numerous, but each of them is indicated in a small group of patients, according to tumor molecular characteristics (*i.e.* EGFR-TKIs and crizotinib in NSCLC).

Few cases of NSCLC patients treated with EGFR-TKI in presence of renal impairment have been recently reported; only few of them described treatment during hemodialysis (Table I).

Rossi *et al.* described two cases of elderly patients affected by chronic renal failure, although not on hemodialysis, successfully treated with gefitinib for lung cancer (17). Only two cases of gefitinib treatment during hemodialysis have been reported until now, besides our case, demonstrating that this TKI can be safely administered and that is not eliminated by dialysis; in fact, almost 90% of the drug was kept in the plasma through hemodialysis (pharmacokinetic pattern was similar to that of patient with normal renal function) and, as in our case, in both of these patients disease was significantly improved by treatment (18-19). In our patient, the benefit from this therapy was very high, with more than 7 years of response duration, without any complication or effects on renal function in the course of dialysis.

Table I. *Case reports of EGFR-TKI treatment in lung cancer patients with renal impairment.*

	Type of EGFR-TKI	Dialysis	Age and PS*	Stage of disease	Line of treatment	Duration of therapy	Best response
Rossi A, Lung Cancer 2005 [17]	Gefitinib	No	70 y PS 2	IV	I	4 months	SD/CB
	Gefitinib	No	72 y PS 1	IV	I	2 ½ months	MR/CB
Shinagawa N, Lung Cancer, 2007 [18]	Gefitinib	Yes	58 y PS 3	IV	I	13 months	PR
Gridelli C, JTO, 2007 [22]	Erlotinib	No	68 y PS 2	IIIB	II	8 months	SD/CB
	Erlotinib	No	63 y PS 2	IV	II	7 ½ months	SD/CB
	Erlotinib	No	76 y PS 2	IV	I	7 ½ months	SD/CB
Togashi Y, JTO, 2010 [20]	Erlotinib	Yes	74 y PS 2	IV	I	NE	SD
	Erlotinib	Yes	74 y PS 3	IIIA	I	NE	PR
	Erlotinib	Yes	69 y PS 2	IV	I	NE	SD
Del Conte A, Anticancer Res, 2014 [19]	Gefitinib	Yes	75 y	IV	I	>18 months	CR
Present case	Gefitinib	Yes	60 y PS 0	IV	II	86 months (7 years)	PR/CB
	Afatinib	Yes	67 y PS 1	IV	III	2 months	SD/CB

*At the start of treatment with EGFR-TKI; PS: Performance status; y: years of age; SD: stable disease; CB: clinical benefit; MR: mixed response; PR: partial response; CR: complete response.

Erlotinib was also demonstrated to be an effective and safe option for treatment in patients with NSCLC undergoing dialysis for chronic renal failure, with similar pharmacokinetic data among three patients on hemodialysis and controls (20). A phase I clinical study by Miller *et al*. explored the pharmacokinetic of erlotinib for solid tumors in 55 cancer patients with moderate hepatic or renal dysfunction; these patients were not undergoing dialysis and erlotinib clearance in the group with renal disease was similar to that of patients without organ impairment (21). A mild renal failure was also present in three cases described by Gridelli *et al*. also in this report erlotinib treatment was well tolerated and did not further compromise renal function (22).

Until now, no data have yet been reported on the safety profile of irreversible EGFR-TKI, such as afatinib, in hemodialysis patients. Our case, despite the short duration of treatment, suggests that this drug has an acceptable tolerability profile in patients with end-stage renal failure undergoing hemodialysis, especially when providing a dose reduction of 25% with respect to the standard, and in this patient did not further compromise the renal function, mantaining the need of hemodialysis three times per week.

Our findings may be particularly useful given the current opportunity to use afatinib as a first-line of treatment for *EGFR*-mutated NSCLC patients, providing an additional option among patients with impaired renal function.

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