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Renal insufficiency is the leading cause of double maintenance (bevacizumab and pemetrexed) discontinuation for toxicity to advanced non-small cell lung cancer in real world setting

Marion Sassier[a,*], Audrey Emmanuelle Dugué[a], Bénédicte Clarisse[a], Paul Lesueur[a], Virginie Avrillon[b], Acya Bizieux-Thaminy[c], Jean-Bernard Auliac[d], Laure Kaluzinski[e], Julie Tillon[f], Gilles Robinet[g], Hervé Le Caer[h], Isabelle Monnet[i], Anne Madroszyk[j], Gabriella Boza[k], Lionel Falchero[l], Pierre Fournel[m], Thomas Egenod[n], Anne-Claire Toffart[o], Nathalie Leiber[a], Pascal Do[a], Radj Gervais[a]

[a] Centre François Baclesse, Caen F-14000, France
[b] Centre Léon Bérard, Lyon F-69008, France
[c] Centre Hospitalier Départemental, La Roche Sur Yon F-85000, France
[d] Centre Hospitalier F. Quesnay, Mantes La Jolie F-78200, France
[e] Centre Hospitalier Public du Cotentin, Cherbourg-Octeville F-50100, France
[f] Centre Hospitalier, Dieppe F-76200, France
[g] Centre Hospitalier Régional Universitaire, Brest F-29200, France
[h] Centre Hospitalier, Draguignan F-83300, France
[i] Centre Hospitalier Intercommunal, Créteil F-94000, France
[j] Institut Paoli Calmettes, Marseille F-13009, France
[k] Centre Hospitalier, Vire F-14500, France
[l] Centre Hospitalier, Villefranche Sur Saône F-69400, France
[m] Institut de Cancérologie Lucien Neuwirth, Saint-Priest en Jarez F-42270, France
[n] Centre Hospitalier Universitaire, Limoges F-87000, France
[o] Centre Hospitalier Universitaire, Grenoble F-38000, France

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ABSTRACT

Objectives: In advanced non-small cell lung cancer (NSCLC), maintenance therapy has emerged as a novel therapeutic reference for patients with non-progressive disease after platinum-based induction chemotherapy. However, the use of double maintenance (DM) with pemetrexed and bevacizumab is still being evaluated in terms of its clinical benefits and safety profile. The objective of this retrospective study was to describe the reasons for DM discontinuation in a real-world setting.
Materials and methods: Patients with advanced non-squamous NSCLC were eligible if they had received at least 4 cycles of induction chemotherapy, followed by at least 1 cycle of DM. They were identified by using the oncology pharmacy database of 17 French centers.
Results: Eighty-one patients who began a DM after induction chemotherapy were identified from September 2009 to April 2013. Among the 78 patients who had stopped DM at the time of the analysis, the main reasons for discontinuation were disease progression (42%), adverse events (33%), and personal preference (8%). The most frequent toxicity responsible for DM discontinuation was renal insufficiency (54%).
Conclusion: For patients with advanced NSCLC eligible for DM therapy, a particular attention should be paid to potential renal failure. Kidney function should be monitored carefully before and during DM to detect and manage early this adverse event.

* Corresponding author at: Centre François Baclesse, Unité de Recherche Clinique, 3 Av. Général Harris, BP 5026, 14076 Caen Cedex 05, France. Tel.: +33 2 31 45 50 02; fax: +33 2 31 45 51 58.
E-mail addresses: marion.sassier@hotmail.fr (M. Sassier), audrey.dugue@baclesse.unicancer.fr (A.E. Dugué), b.clarisse@baclesse.unicancer.fr (B. Clarisse), paul.lesueur89@gmail.com (P. Lesueur), r.gervais@baclesse.unicancer.fr (R. Gervais).

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1. Introduction

In advanced non-small cell lung cancer (NSCLC), first-line induction by platinum-based doublet chemotherapy followed by maintenance therapy has emerged as a novel therapeutic reference for patients with non-progressive disease after induction, i.e. about 60% of patients. Two separate maintenance strategies have evolved: the introduction of an additional agent immediately after completion of induction chemotherapy (switch maintenance), or the continuation of the non-platinum partner initially introduced during induction (continuation maintenance) [1]. Both strategies have been shown to improve Progression Free Survival (PFS) and/or Overall Survival (OS) for patients with at least stable disease after induction chemotherapy.

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) inhibitor monoclonal antibody, and pemetrexed, a multitarget antifolate agent, have both proven to be important components in the first-line induction and maintenance setting. Thus, bevacizumab was associated to first-line chemotherapy followed by bevacizumab continuation maintenance until disease progression in two phase III studies [2,3]. The JMEN study examined pemetrexed as switch maintenance therapy after platinum-based chemotherapy [4], while the PARAMOUNT study compared continuation maintenance by pemetrexed with best supportive care [5,6].

Recent phase III studies have also investigated the value of double maintenance (DM) by bevacizumab and pemetrexed administered every 21 days. In particular, the PointBreak study compared a regimen of carboplatin, pemetrexed plus bevacizumab followed by pemetrexed plus bevacizumab maintenance, with a regimen of carboplatin, paclitaxel plus bevacizumab followed by bevacizumab maintenance [7]. From the randomization before induction, median OS was similar in both arms and the PFS was statistically significantly longer in the DM arm. In a preplanned analysis among the maintenance population, PFS and OS were improved in patients receiving DM vs. bevacizumab alone (respectively 8.6 vs. 6.9 months and 17.7 vs. 15.7 months). The AVAPERL study compared continuation maintenance with bevacizumab monotherapy and bevacizumab plus pemetrexed. The DM arm had a significantly longer PFS, as measured from the time of randomization after induction (7.4 vs. 3.7 months; $P<0.001$) and from the start of induction by platin, pemetrexed, and bevacizumab (10.2 vs. 6.6 months; $P<0.001$). OS from the start of induction was also numerically longer by nearly 4 months for DM, although the difference was not significant (19.8 vs. 15.9 months; $P=0.32$) [8,9].

The value of maintenance therapy is now statistically established, but the use of DM is still controversial while waiting for additional studies assessing its clinical benefits and safety profile. Currently, DM is not standard practice but remains an option used by some physicians with selected patients.

The purpose of our retrospective study was to describe in a real-world setting the frequency of DM discontinuation for adverse events, together with the prevalence and type of toxicities occurring during DM.

2. Patients and methods

2.1. Eligibility

All patients older than 18 years with advanced non-squamous NSCLC were eligible if they had received at least 4 cycles of induction chemotherapy with platinum, pemetrexed, and bevacizumab, followed by at least 1 cycle of DM (pemetrexed and bevacizumab).

Patients were identified from September 2009 to April 2013 by using the oncology pharmacy database of 17 French centers.

The study was conducted in accordance with the Good Clinical Practice guidelines. All patients were monitored for survival and DM discontinuation until June 2014.

2.2. Endpoints

All charts were retrospectively reviewed to collect clinical and laboratory data, including renal function (before induction and before DM) assessed by estimated glomerular filtration rate (eGFR), calculated by the abbreviated Modification of Diet in Renal Disease (aMDRD) formula from serum creatinine. In this multicenter observational retrospective study, the primary objective was to describe the reasons for DM discontinuation defined as definitive interruption of any of two or both drugs. The associated reason was determined by the referring physician and classified as "disease progression", "adverse event" or "other reason". Treatment following DM discontinuation for adverse events and OS were also assessed.

2.3. Statistical analysis

Categorical data were described by frequencies and percentages, while numerical data were described by mean and standard deviation or median and extreme values if necessary. OS was estimated with the Kaplan–Meier method.

The probability to stop DM for a given adverse event was estimated over time by the Fine & Gray method, assuming that stopping for another reason was a competing risk [10]. The time point of discontinuation was set at 20 days after the last injection. Because the proportional hazard assumption was not verified, we only tested the probability of discontinuing DM for renal insufficiency by a Chi squared or Fisher's exact test, according to the following factors: initial metastatic status, older than 65 years, history of cardiovascular disease, impaired (grade 1 and above according to the National Cancer Institute Common Terminology Criteria for Adverse Events CTCAE v.4) renal function before induction and before DM, and at least one cycle of cisplatin during induction chemotherapy.

Alpha risk was set at 0.05 for each statistical analysis. All figures and analyses were produced by using the R software [11].

3. Results

The study population consisted of 81 patients identified in the participating centers (Table 1). Thirty-two (46%) had an impaired renal function (only grade 1 or 2) before induction treatment.

Table 1
Baseline characteristics ($n=81$).

	Description	Number of patients
Age (*y*) at induction, median, range	58 [28–71]	81
Male gender, *n* (%)	44 (54%)	81
Disease stage at diagnostic		81
1A	2 (2%)	
1B	2 (2%)	
2B	1 (1%)	
3A	3 (4%)	
3B	5 (6%)	
4	68 (84%)	
Adenocarcinoma	79 (98%)	81
Renal function before induction aMDRD eGFR (ml/min/1.73 m^2)		69
≥90 (gr 0)	37 (54%)	
89–60 (gr 1)	31 (45%)	
59–30 (gr 2)	1 (1%)	
Months from diagnosis to induction start	1.2 [0–42]	77

y, year; eGFR, estimated glomerular filtration rate; aMDRD, abbreviated Modification of Diet in Renal Disease.