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Maintenance treatment in non-small cell lung cancer (NSCLC): pro

Francesca Mazzoni, Alice Lunghi, Paolo Petreni, Agnese Vannini, Elisa Pellegrini, Fabiana Letizia Cecere, Francesco Di Costanzo

SC Oncologia Medica, Department of Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

Summary. Non-small cell lung cancer (NSCLC) is the second tumor in incidence worldwide and, at present, remains the leading cause of cancer death. According to the Italian Drug governance, although the incoming knowledge reached during these years, the backbone treatment of the advanced stages of lung cancer remains standard chemotherapy. Platinum-based chemotherapy, prolonged from four to six cycles, is the standard therapy for all the subtypes of NSCLC without Epidermal Growth Factor Receptor (EGFR) mutation. According to the several guidelines, second line therapy must be composed by a single agent drug. During recent years a great attention has been given to the chemotherapy free window which existed between the first and the second line, in case of stable disease (SD) or objective response (OR). Several therapeutic maintenance strategies have been studied, both in continuing the strategy chosen for the first line and in changing the drug, with a no cross-resistant agent, stopping the platinum salt anyway. Although a number of these studies demonstrated that maintenance therapy improved progression free survival (PFS) compared with observation, only few had a significant overall survival (OS) benefit. Pemetrexed, utilized both in patients treated with this drug in first line and as switch maintenance, and bevacizumab, in continuation maintenance setting, are the only drugs which have been shown able to prolong OS in adenocarcinoma histology. Despite these positive results, implementation of maintenance therapy in NSCLC remains debated, and at this moment there are no data comparing continuation and switch maintenance treatment.

Key words: non-small cell lung cancer, maintenance therapy, chemotherapy, pemetrexed, continuation maintenance, switch maintenance

«Terapia di mantenimento nel carcinoma del polmone non a piccole cellule: pro»

Riassunto. Il carcinoma del polmone non a piccole cellule (NSCLC) è il secondo tumore per incidenza nel mondo e rimane la principale causa di morte per cancro. Nonostante l'incremento delle conoscenze ottenuto negli ultimi anni, il cardine del trattamento degli stadi avanzati del NSCLC rimane la chemioterapia. La chemioterapia, costituita da un derivato del platino associato ad un farmaco di terza generazione, effettuata per quattro-sei cicli, è considerata la terapia standard in prima linea per tutti i sottotipi di NSCLC che non presentano mutazioni del gene codificante per il recettore del fattore di crescita epidermico (EGFR). Secondo numerose linee guida, la chemioterapia di seconda linea prevede invece la somministrazione di un singolo farmaco. Negli ultimi anni è stata valutata la possibilità di eseguire un trattamento anche nell'intervallo libero da terapia che si trovava fra la fine della prima linea e l'inizio della seconda, nel caso di malattia stabile (SD) o in risposta obiettiva (OR). Sono state studiate due strategie di terapia di mantenimento: una prevede di proseguire il farmaco utilizzato in prima linea in associazione con il derivato del platino e l'altra di cambiare il chemioterapico con un agente non cross-resistente, in ogni caso sospendendo il sale di platino. Sebbene molti studi abbiano dimostrato che la terapia di mantenimento determini un beneficio statisticamente significativo

in termini di sopravvivenza libera da progressione (PFS) rispetto alla sola osservazione, solo pochi sono riusciti a confermare tale vantaggio anche in termini di sopravvivenza globale (OS). Il pemetrexed, utilizzato sia in pazienti già trattati durante la prima linea, sia in coloro che non lo avevano ricevuto in precedenza, ed il bevacizumab, proseguito dopo la sospensione della terapia di prima linea, sono gli unici farmaci che si sono dimostrati in grado di prolungare la OS nei pazienti affetti da adenocarcinoma. Nonostante questi risultati positivi, l'utilizzo della strategia di mantenimento nel NSCLC rimane ancora dibattuta, ed al momento non ci sono dati di confronto fra le due strategie di mantenimento studiate.

Parole chiave: carcinoma del polmone non a piccole cellule, terapia di mantenimento; chemioterapia

Introduction

Non-small cell lung cancer (NSCLC) is the second tumor in incidence for both sexes worldwide and, at present, remains the leading cause of cancer death, with a slight prevalence for male patients (1). Treatment for advanced NSCLC had seen some changes during the last decade in part due to the incoming presence of new drugs, in part to the numerous molecular analyses which allow distinguishing various subtypes of lung cancer. According to the Italian Drug governance, although the incoming knowledge reached during these years, the backbone treatment of the advanced stages of lung cancer remains, in almost cases, standard chemotherapy (2). At present, the only exception to the use of chemotherapy for the first line treatment is the case of Epidermal Growth Factor Receptor (EGFR) mutated NSCLC, for whom the use of an oral tyrosine kinase EGFR inhibitors (TKIs), erlotinib or gefitinib or afatinib, are the recommended choice reaching a progression free survival (PFS) of nearly 9-11 months (3-5). Platinum-based chemotherapy, prolonged from four to six cycles, remains the standard therapy for all the other subtypes of NSCLC, reaching a PFS of nearly 3-5 months (6, 7). Platinum salt, according to the patient clinical condition and to the histological subtype, can be accompanied by a third generation antineoplastic agent such as gemcitabine, vinorelbine or taxanes (8-11). Moreover for non-squamous NSCLC other options available are pemetrexed, to add to the platinum salt, and bevacizumab, to add to the platinum doublet (12, 13). According to the several guidelines, second line therapy must be composed by a single agent drug (2): patients with EGFR mutated NSCLC must receive an EGFR-TKI (14, 15); in the presence of anaplastic lymphoma kinase (ALK) rearrangements the correct choice should be the ALK-TKI crizotinib (16); actually other molecular target as Kirsten Rat Sarcoma (KRAS) mutation or Reactive Oxygen Species 1 (ROS1) rearrangements are drug-orphan targets, even though there is a growing pre-clinical and clinical research upon them (17). During last years a great attention has been given to the chemotherapy free window which existed between the first and the second line, in case of stable disease (SD) or objective response (OR). Several therapeutic maintenance strategies have been studied, both in continuing the strategy chosen for the first line and in changing the drug, with an agent no cross-resistant, stopping the platinum salt anyway. Here we describe in summary the various options studied demonstrating a positive outcome in NSCLC.

Continuation maintenance

Continuation maintenance strategy consists in continuing administration of at least one of the antineoplastic agents utilized in the first line therapy until progression disease (PD) or unacceptable toxicity. The biological rational of this strategy is trying to exploit the maximum efficacy from chemotherapy in responder patients, however reducing toxicity. Several drugs had been investigated for this indication with different results (table 1): some positive leading to the approval for Italian drug Agency (AIFA), such as pemetrexed or bevacizumab; some positive but judged not relevant for AIFA, as the combination pemetrexed/bevacizumab; some negative like gemcitabine.

Table 1. Trials of continuation maintenance therapy for advanced NSCLC.

Trial	N. patients enrolled	Maintenance therapy	PFS in months from random (p)	OS in months from random (p)
Brodowicz, 2006 (23)	138	gemcitabine	3.6	10.2
		vs	(<0.01)	(0.72)
	68	placebo	2.0	8.1
Belani, 2010 (24)	128	gemcitabine	3.9	8.0
		vs	(0.575)	(0.838)
	127	placebo	3.8	9.3
Perol, 2012 (25)	154	gemcitabine	3.8	12.1
		vs	(0.001)	(0.38)
	155	placebo	1.9	10.8
Paz-Ares, 2013 (PARAMOUNT) (18)	359	pemetrexed	4.1	13.9
		vs	(<0.0001)	(0.0195)
	180	placebo	2.8	11.0
Barlesi, 2014 (AVAPERL) (21)	128	pemetrexed+bevacizumab	7.4	17.1
		vs	(<0.001)	(0.29)
	125	bevacizumab	3.7	13.2
Patel, 2013 (PointBreak) (22)	292	pemetrexed+bevacizumab	6.0	12.6
		vs	(0.012)	(0.949)
	298	bevacizumab	5.6	13.4
Sandler, 2006 (ECOG 4599)* (19)	434	bevacizumab	6.2	12.3
		vs	(0.001)	(0.003)
	444	placebo	4.5	10.3
Reck. 2010 (AVAIL)* (20)	345	bevacizumab 7.5 mg/kg vs	6.7 (0.0003)	13.6 (0.420)
	351	bevacizumab 15 mg/kg vs	6.5 (0.0456)	13.4 (0.761)
	347	placebo	6.1	13.1

Pemetrexed

The phase III PARAMOUNT study was designed to assess the efficacy of the continuation maintenance therapy with pemetrexed in patient with non-squamous NSCLC after four cycles of cisplatin doublet with OR or SD. A total of 539 patients were randomized in a 2:1 ratio arms to receive respectively pemetrexed or placebo until PD. With a median number of 4 cycles administered (1-16 range) the primary end point was met reaching a median PFS of 4.1 months versus 2.8 months observed for the placebo group (Hazard Ratio, HR, 0.62; P<0.0001). A statistical significant benefit for the experimental arm was also observed for the overall survival (OS): 13.9 months vs 11 months (P=0.0195). The median OS measured from induction was 16.9 months for pemetrexed and 14.0 months for placebo (HR 0.78; P=0.0191). A subgroup analysis showed that all patients benefit from this strategy: the benefit appeared higher in responder patients (median PFS 4.1 months vs 2.8 months; HR 0.48) than in stable disease patients (median PFS 4.1 months vs 3.0 months; HR 0.74). The toxicity profile of the experimental arm revealed a significant higher incidence of grade 3-4 fatigue (4.7 % vs 1.1 % for placebo arm), anemia (6.4 % vs 0.6 %) and neutropenia (5.8 % vs 0 %); although health related quality of life (QoL) was not affected (18).

Bevacizumab

The phase III Eastern Cooperative Group (ECOG) 4599 study evaluated the role of bevacizumab in advanced non-squamous NSCLC. A total of 878 patients were randomized in a 1:1 ratio to received chemotherapy with paclitaxel and carboplatin alone or paclitaxel and carboplatin and bevacizumab for a total of six cycles. In the arm with bevacizumab the drug was then administrated until PD or intolerable toxic effects. The primary end point, OS, was met with 12.3 months vs 10.3 months in the arm without bevacizumab (HR 0.79; P=0.003). Also PFS was higher in the arm with bevacizumab (6.2 months vs 4.5 months; HR 0.66; P<0.001). Severe adverse events were significantly higher in the bevacizumab arm, and also the deaths related to toxic effect of treatment were more frequent for bevacizumab group (P=0.001) (19).

The AVAIL study randomized 1043 patients to receive six cycles of cisplatin and gemcitabine plus bevacizumab 15 mg/kg or bevacizumab 7,5 mg/Kg or placebo. Bevacizumab or placebo were administrated until PD. The primary end-point, PFS, was higher in the bevacizumab groups. For low dose bevacizumab arm median PFS was 6.7 months vs 6.1 months with placebo (HR 0.75; P=0.0003); for high dose bevacizumab vs placebo median PFS was 6.5 months vs 6.1 months (HR 0.85; P=0.0456). The OS was not significantly increased with bevacizumab (P=0.420 for the 7.5 mg/Kg group; P=0.761 for the 15 mg/Kg group), versus placebo. Incidence of grade 3 or greater adverse events was similar across arms (20).

Pemetrexed plus bevacizumab

The phase III AVAPERL study explored the role of pemetrexed in combination with bevacizumab versus bevacizumab alone. The study design consist in a four cycles first line with a triplet of cisplatin, pemetrexed and bevacizumab: 253 patients without PD were randomized in 1:1 ratio to the two arms. Primary end point was PFS and was met with 7.4 months for the combination arm, with a median of seven cycles, vs 3.7 months observed in the bevacizumab alone group, with a median of five cycles (HR 0.48; P<0.001). Median OS superiority for the combination arm was not reached, therefore the study was not powered for it. Severe toxicities were more common in the combination arm, without modifications of QoL (21).

The phase III POINTBREAK study had a two arms design: in the first arm patients were submitted to a first line with carboplatin, pemetrexed and bevacizumab for four cycles and a subsequent maintenance therapy with pemetrexed and bevacizumab; the control arm was the standard bevacizumab containing triplet (carboplatin and paclitaxel) administered for four cycles with bevacizumab alone maintenance. The primary end point, median OS, was not met: the combination arm reached an OS of 12.6 months vs 13.4 months with control arm (P=0.949). Median PFS was instead slightly significantly higher in the pemetrexed/bevacizumab arm (6 months vs 5.6 months; HR 0.83; P=0.012) (22).

Gemcitabine

Three clinical trials investigate the maintenance role of gemcitabine in patients with OR or SD after first line therapy combination with platinum salts; all these trials were designed with several limitations affecting results: high proportion of patients with poor performance status, elevated number of delayed therapies, inappropriate instrumental disease evaluations, misused second line therapies. In the Investigators of Central European Cooperative Oncology Group trial the Time To Progression (TTP) was significantly longer for the gemcitabine arm vs placebo arm after four cycles of cisplatin/gemcitabine chemotherapy, but there was no statistically significant difference in OS (23). A second phase III trial with an analogue design, but with a first line containing carboplatin, showed no improvement in OS and in PFS (24). The other phase III trial investigated the maintenance role of gemcitabine or erlotinib vs placebo, with a three arms design, in non-PD patients after 4 cycles of cisplatin/gemcitabine. Pre-planned second line for all groups was pemetrexed. The primary end point, PFS, was met but there was no improvement in OS; a trend towards a statistical significant benefit in PFS and OS was observed in patients who achieved an OR after the induction therapy (25).

Switch maintenance

Switch maintenance strategy consist in the administration of a new antineoplastic agent that was not part of the induction therapy and involves a potentially non-cross-resistant agent starting after the first line therapy until PD or unacceptable toxicity. This strategy, in theory, could permit to dead the more cancer cells as possible which have not been destroyed by the induction therapy. This plan has also the advantage to utilize the more drugs as possible when patients' performance status remains good. In this setting also several drugs had been investigated (table 2): with positive results leading to the approval for Italian drug Agency (AIFA) there is only pemetrexed; with positive results, judged not relevant for AIFA, there is erlotinib; negative results were observed for docetaxel and gefitinib.

Pemetrexed

A phase III trial published in 2009 investigating the use of pemetrexed until PD after four cycles of chemotherapy containing a platinum compound and gemcitabine or a taxane, in patients with disease control. After a median number of 5 cycles, pemetrexed achieved a median PFS of 4.3 months vs 2.6 obtained by placebo (HR 0.50; P<0.0001) and, furthermore, significantly improved OS compared with placebo, reaching 13.4 vs 10.6 months (HR 0.79; P=0.012). This gaining was more evident in patients with non-squamous histology: median PFS of 4.5 vs 2.6 months (HR 0.44; P<0.0001) and median OS of 15.5 vs 10.3 months (HR 0.44; P<0.0001). Toxicity evaluation revealed higher incidence of grade 3-4 fatigue and neutropenia than with placebo, without treatment related deaths (26).

Table 2. Trials of switch maintenance therapy for advanced NSCLC.

Trial	N. patients enrolled	Induction therapy	Maintenance therapy	PFS in months from random (p)	OS in months from random (p)
Fidias, 2009 (29)	153	carboplatin + gemcitabine	docetaxel immediate	5.7	12.3
			vs	0.71 (0.0001)	0.84 (0.0853)
	156		docetaxel delayed	2.7	9.7
Cappuzzo, 2010 (SATURN) (27)	437	platinum-based	erlotinib	12.3 weeks	12.0
			vs	0.71 ((<0.0001)	0.81 (0.0088)
	447		placebo	11.1 weeks	11.0
Ciulenau, 2009 (JMEN) (26)	441	platinum-based (no pemetrexed)	pemetrexed	4.3	13.4
			vs	0.50 ((<0.0001)	0.79 (0.012)
	222		placebo	2.6	10.6
Johnson. 2013 (ATLAS) (28)	370	platinum-based +bevacizumb	beva+erlotinib	4.8	14.4
			vs	0.71 ((<0.001)	0.92 (0.53)
	373		beva+placebo	3.7	13.3
Gaafar, 2011 (31)	86	platinum-based	gefitinib	4.1	10.9
			vs	0.91 (0.0015)	0.83 (0.2)
	87		placebo	2.9	9.4
Zhang, 2012 (INFORM) (32)	148	platinum-based	gefitininb	4.8	18.7
			vs	0.42 (<0.0001)	0.84 (0.26)
	148		placebo	2.6	16.9
Perol, 2012 (25)	155	cisplatin+ gemcitabine	erlotinib	0.69	11.4
			vs	(0.69) (0.003)	0.87 (0.26)
	155		placebo	1.9	10.8

Erlotinib

Three randomized phase III studies investigated erlotinib as a switch maintenance therapy. The SATURN trial was conducted in European population and explored the use of erlotinib vs placebo in 884 unselected patients for EGFR status without disease progression after four cycles of platinum-based chemotherapy (bevacizumab was not permitted). Erlotinib PFS was significantly longer, comparing with placebo (12.3 vs 11.1 weeks; HR 0.71; P<0.0001), both for EGFR mutated and for EGFR wild type patients. There was also a slight, but significant, increase in OS (12.0 vs 11.0 months; HR 0.81; P<0.0088). A subgroup analysis, not planned, showed longer OS for those patients who, after the first line chemotherapy, experienced SD than responder patients. Serious adverse events, grade 3-4, were more common with erlotinib than placebo, in particular skin rash (9% vs 0%) and diarrhea (2% vs 0%) (27).

The ATLAS trial was a phase IIIb study investigating the addition of erlotinib in the maintenance therapy with bevacizumab in patients without disease progression after a first line composed by platinum doublet and bevacizumab. The addition of erlotinib produced a small but significant benefit in PFS (4.8 vs 3.7 months; HR 0.71; P<0.001), which was the primary end point; this trend was not confirmed for OS (P=0.53) (28).

The third trial compared the maintenance therapy with gemcitabine in patients without progression after four cycles of cisplatin based chemotherapy, or the switch therapy with erlotinib in comparison to observation. As discussed before in the continuation maintenance paragraph, both maintenance therapies prolonged PFS, primary end point, with a modest benefit: 3.8 vs 1.9 months for gemcitabine (HR 0.56; P<0.001) and 2.9 vs 1.9 months for erlotinib (HR 0.69; P=0.003). No benefit in terms of OS was seen for both maintenance therapies (25).

Docetaxel

One of the first phase III trial conducted with the aim to investigate the role of maintenance chemotherapy after induction platinum based first line was done with the drug docetaxel. The study, published by Fidias in 2009, was design to compare, after four cycles of carboplatin and gemcitabine, the immediate therapy with docetaxel, until PD or up to six cycles, and the same chemotherapy begun at PD. The primary end point was not met with a difference in OS that was not statistically significant (12.3 months for immediate vs 9.7 for delayed docetaxel; P=0.0853). There was therefore a significant improvement in PFS (5.7 months for immediate vs 2.7 for delayed docetaxel; P=0.0001); no difference in terms of QoL was recorded (P=0.76) (29).

Gefitinib

Gefitinib maintenance therapy was investigated firstly in Japanese population. The trial was conducted in 604 unselected patients randomly assigned to six cycles of platinum doublet first line chemotherapy or to three cycles of the same chemotherapy and subsequent therapy with gefitinib in those patients with SD or PR, until PD. There was a small significant benefit in terms of PFS (4.6 vs 4.3 months; HR 0.68; P<0.001), however there was no difference for OS, the primary end point (P=0.11) (30).

A second trial was then conducted in western population, but it was prematurely stopped due to poor accrual. The design of the trial consist in two arms comparing the use gefitinib with observation after an induction first line platinum based chemotherapy, performed from two to six cycles. OS was not significantly improved (10.9 vs 9.4 months; P=0.2); therefore there was a little benefit for PFS (4.1 vs 2.9 months; HR 0.61; P=0.0015). Nevertheless the study population was unselected for EGFR status (31).

The INFORM trial was a phase III study investigating the role of gefitinib as a switch maintenance therapy after four cycles of cisplatin doublet in Asian patient NSCLC, unselected for EGFR, without PD; the control arm was placebo-based. PFS, which was the primary end point of the trial, was significantly longer for patients treated with gefitinib (4.8 vs 2.6 months; HR 0.42; P<0.0001) and also QoL was significantly better in the gefitinib arm. However OS was not superior for the experimental arm (P=0.26) (32).

Discussion

Nowadays there is a great debate worldwide about the first line chemotherapy in NSCLC. Excluding EGFR mutated patients, for whom the first choice should be an EGFR-TKI (3-5), a great attention has been focused on the duration of the first line. In particular many studies investigated how many cycles are the best option to propose to patients affected by locally advanced or metastatic NSCLC: four, six or more (6, 7); and furthermore which is the right platinum compound to use and which are the best drugs to associate (8-13). After four to six cycles of first line chemotherapy approximately two thirds of patients have non progressive disease; continuation of platinum-based combination regimens beyond 4-6 cycles results in heightened toxicities and diminishes quality of life without providing a survival advantage. International chemotherapy guidelines, and Italian guidelines too, advice to begin a platinum doublet, for fit patients, in first line choosing it on the base of the histology, the performance status of the patients and their comorbidities. First line chemotherapy should be delayed for no more than four cycles for non-responder patients and no more than six in responders (2). Another key point raised up during last years is the maintenance strategy, consisting in continuing chemotherapy after the induction first line, containing the platinum salt. Several large phase III trials have evaluated the benefits of various continuation and switch maintenance strategies; although a number of these studies demonstrated that maintenance therapy improved PFS compared with observation, only few had a significant OS benefit. In summary, only pemetrexed, utilized both in patients treated with this drug in first line and as switch maintenance (18, 26), and bevacizumab, in continuation maintenance setting (19), are currently the only drugs which have been shown, in phase III randomized trials, able to prolong OS in adenocarcinoma histology. In particular, in PARAMOUNT study, pemetrexed maintenance could reach 16.9 months of survival since the beginning of the induction therapy, in comparison to the control arm composed by the observation only; therefore maintenance therapy with pemetrexed allows to gain 3 months OS advantage and 2 months in PFS (18). Even if the majority of these trials included in their design a second line therapy after PD, affecting probably OS results, maintenance strategy is the first evidence that continuing antineoplastic therapy beyond the first line can produce a benefit both for survival parameters and for QoL. Despite these positive results, implementation of maintenance therapy in NSCLC remains debated.

The values of maintenance therapy are the opportunity to decrease development of chemotherapy resistance, to treat a major number of patients and to maximize the efficacy of first line chemotherapy. However the same therapy prevents some patients from having a drug holiday, adds costs, exposes patients to toxicities and eliminates from second-line efficacy drugs.

According us, the maintenance therapy is a relevant option to discuss with patient, even considering the fact that some patients could not be able to receive a second line anymore and that would have anyway poor results. Treatment choice should be based on EGFR and ALK status, histology, response to front line therapy and patient preference. In EGFR wild type maintenance therapy is not recommended for patients with low performance status; instead in EGFR mutated patients EGFR TKIs are the best option not dependent from PS.

The role of maintenance treatment is still under investigation and at this moment there are no data comparing continuation and switch maintenance therapy.

Only few clinical, molecular and histological factors can actually help providers to deciding whether to continue therapy (i.e. response to first line therapy, toxicity related to the treatment, comorbidities and preferences, squamous cell carcinoma or adenocarcinoma histology, presence or absence of molecular mutations).

The identification of predictive factors to select patients who will benefit from maintenance therapy compared to a delayed treatment is essential in order to obtain treatment optimization in term of patient's benefit and costs. For this reason future trials on maintenance therapy should include molecular tumor analysis and sample collection during the treatment.

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Address: Francesca Mazzoni, MD
SC Oncologia Medica, Department of Oncology,
Azienda Ospedaliero-Universitaria Careggi,
Largo Brambilla 3, 50134 Florence, Italy
Tel. +39 055 7949648
Fax +39 055 7948394
E-mail: francescamazzoni@hotmail.com