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Maintenance Therapy after First Line Chemotherapy Shows Benefit in Advanced Non-Small Cell Lung Cancer

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Abstract

Background: Maintenance therapy refers to an extended duration after frontline induction chemotherapy (CT) for patients with advanced non-small cell lung cancer (NSCLC). Several recent randomised controlled trials (RCTs) showed a survival benefit for maintenance therapy, especially for EGFR tyrosine-kinase inhibitors (TKIs), but conflicting results have been published. We performed a meta-analysis of all RCTs published either as articles or as abstracts.

Patients and Methods: A PubMed query using several keywords simultaneously (NSCLC, maintenance, RCT, survival) found 79 references. Abstracts from proceedings of ASCO and ESMO meetings were also reviewed. References were cross-checked. Outcomes were overall survival (OS) and progression free survival (PFS), both assessed by hazard ratios (HR) and their 95 % confidence interval (CI). By convention, HRs lower than 1 indicated increased survival with maintenance therapy or a lower incidence of adverse effects, compared with controls. We used a fixed effect model when heterogeneity was absent and random effect model when present. We used EasyMA software.

Results: Thirteen RCTs were included with IFCT-GFPC trial used twice since it assessed 2 maintenance therapies in parallel, gemcitabine and erlotinib. The MA included 5251 patients (median age 61 years, 4261 stage IV, 913 stage III diseases, 2929 adenocarcinomas, 983 squamous cell carcinomas). For OS (14 sub-studies), a significant reduction in mortality favouring maintenance was observed (HR OS 0.86; CI 0.80-0.92; fixed effect model). For PFS (13 sub-studies), the overall HR was 0.65 (CI 0.58-0.73; random effect model). OS improved with continuation maintenance (6 RCTs, HR 0.89, CI 0.78-1.03) and switch maintenance (3 RCTs, HR 0.85, CI 0.75-0.98). For targeted therapies, OS also increased (5 RCTs, HR 0.85, CI 0.77-0.93). Anaemia, thrombocytopenia and neutropenia were significantly more frequent with maintenance chemotherapy, and skin rashes with EGFR TKIs.

Conclusion: Maintenance therapy with either continuation or switch chemotherapy or EGFR TKIs significantly improved OS and PFS. The benefit-to-risks balance of these 3 types of maintenance should be compared.

Introduction

Lung cancer is a major cause of death worldwide. About 80 to 85 % of lung cancers are non-small cell lung cancers (NSCLC), which represent the leading cause of cancer mortality in developed countries. Advanced NSCLC can be either metastatic (stage IV) or recurrent or locally advanced (stage III) but not amenable to curative therapy. The current standard first-line therapy for advanced NSCLC consists of 4-6 cycles of platinum-based doublet chemotherapy. Such a treatment leads to a clinical response or stable disease in 70-80 % of patients. However, the prognosis of advanced NSCLC remains poor, with a one-year survival ranging from 34 to 44 % and a 5-year survival of less than 5 %. In an attempt to increase survival, maintenance therapy has been extensively studied during the last ten years. Maintenance therapy refers to an extended duration of treatment after frontline induction chemotherapy. Maintenance therapy can be performed either with a drug used during the induction phase of chemotherapy (continuation maintenance) or with another drug (switch maintenance). In 2009, when the American Society of Clinical Oncology (ASCO) updated its guidelines for the treatment of NSCLC, maintenance therapy remained debated. Recently, two drugs (pemetrexed, erlotinib) have been approved for maintenance therapy of non-progressing NSCLC after first-line therapy since they showed significant improvement in Overall Survival (OS). Few meta-analyses (MAs) have been published, the first one in 2009 assessed only some studies using continuation or switch chemotherapy [1]. A recent MA by Zhang et al. [2] concluded to a survival benefit of maintenance therapy compared with placebo or observation but did not include the studies presented at ASCO 2010 and 2011 meetings [3]. In addition, this MA did not provide evidence that continuation maintenance improved survival. Therefore, we performed an updated MA of all studies either published or presented at conferences dealing with all types of maintenance therapy in NSCLC (continuation or switch chemotherapy, targeted therapy). The aim of our MA was to assess the benefits (in terms of OS and PFS improvement) and risks (adverse events) of maintenance therapies, taken overall or separately.

Material and Methods

Search methods for identification of the studies

We performed our meta-analysis according to a predefined written protocol. Studies were selected using several sources. The main source was a PubMed query updated on April 2015 using keywords simultaneously (non-small cell lung cancer, maintenance, randomised controlled trial, survival). An EMBASE query was also performed, and also the screening of Cochrane database of systematic reviews. Both of these complementary searches did not retrieve additional references. Abstracts from ASCO and ESMO meeting proceedings from 2009 to 2015 were also reviewed. Finally, we cross-checked all references from all papers retrieved.

Publication selection

We included in our meta-analysis only randomised controlled trials (RCTs) comparing maintenance therapy with placebo or no treatment (best supportive care in both groups) in adult patients with stage IIIB or IV NSCLC. All RCTs had to assess either overall survival (OS) or progression free survival (PFS) or both. Accepted maintenance therapies were chemotherapies or authorised targeted agents. Maintenance therapy could consist of continuation maintenance prolonging one drug (except platinum) used during induction chemotherapy such as gemcitabine, or switch chemotherapy introducing a new drug such as pemetrexed or adjunction of a biotherapy such as erlotinib. Studies were included when maintenance therapy was restricted to patients without disease progression after induction chemotherapy. Studies assessing induction chemotherapy with systematic concurrent chest radiation were excluded except when they included only stage IV diseases [4-5]. The study by Hanna et al. was thus excluded since it comprised 40 % stage IIIA patients, 60 % stage IIIB and no stage IV. By contrast, the 2 RCTs adding a targeted therapy or a placebo to bevacizumab as a maintenance therapy, were included (ATLAS, AVAPERL). For PARAMOUNT study, preliminary data concerning OS were recently published [6].

Data collection and analysis

The present MA relied on published articles and abstracts, not on individual patient data. Each eligible publication was assessed by two reviewers independently (GDG more specifically in charge of the clinical aspects and BU more specifically in charge of the methodological aspects) using a predefined data collection form. For each study, this data form collected information such as median age, gender, clinical stages (IIIB or IV), ECOG performance status, pathological types (adenocarcinoma, squamous or other), number of cycles of induction chemotherapy, adverse events (overall or grade 3/4). Any disagreement was resolved by discussion. Both reviewers assessed the methodological quality of RCTs (quality of random allocation, concealment, description of drop-outs and withdrawals), but a quality score such as Jadad score was not used for weighting of the meta-analysis since no such score has received general agreement for this purpose and all RCTs were of rather similar quality.

Statistical analysis

Hazard Ratios (HRs) and their 95 % Confidence Interval (CI) were extracted directly from the articles or provided by authors after request or obtained by extrapolation from survival curves. A fixed effect model was used when heterogeneity between studies was absent and a random effect model when it was present. We used EasyMA software (http://www.spc.univ-lyon1.fr/easyma.net/). This software is available online (Department of Clinical Pharmacology, Cardiology hospital, Lyon, France). The statistical analysis was performed by Dr. Patrick Nicolas. By convention, a HR lower than 1 for OS or PFS meant that the corresponding study favoured maintenance therapy and a HR higher than 1 meant that maintenance therapy had a detrimental effect, as was the case for instance for several adverse effects. A linear regression model was applied to the HR OS and PFS values for each study and their corresponding differences between the groups treated with active drug or placebo or best supportive care in each study in median OS and PFS. P-values lower than 0.05 were considered statistically significant (two-tailed test).

Results

The flow chart of this MA is shown in Figure 1. Eighty-nine publications were retrieved from PubMed, but 82 papers were excluded (18 were reviews, 41 were phase III RCTs or papers out of the scope of the MA, 3 had an incorrect study design, 19 were phase I/II studies, 1 was a letter with insufficient information). In addition, we gathered 6 abstracts from ASCO meeting proceedings 2009-2015). Consequently, 13 phase III RCTs were included [3,5,7-17]. The study by Pérol**10** was included twice since it had 3 arms (observation, gemcitabine maintenance, erlotinib maintenance), leading to 14 sub-studies.

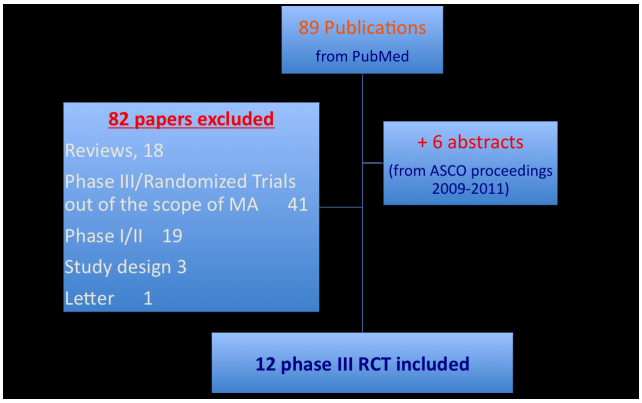

Figure 1: Flow-chart of the meta-analysis

The main characteristics of patients included in the studies are presented in the Table 1. The total number of patients included in the MA was 5,251, with a median age of 61 years. There were 4,261 patients with stage IV disease and 913 with stage III disease. Adenocarcinomas largely predominated (2,929 compared with 983 squamous cell carcinomas). Continuation maintenance with chemotherapy was represented by gemcitabine in 3 RCTs [9-11], paclitaxel in one study and pemetrexed in the last two studies [16,6,7] Switch maintenance with chemotherapy was represented by vinorelbine, docetaxel and pemetrexed, each in one study [5,12,13]. Maintenance with targeted therapies used erlotinib in 3 studies [10,14,18] and gefitinib in 2 studies [8,17]. All first-line chemotherapies included a platinum derivate.

References	No	age	III	IV	Adenoc	SCC		Initial	Maintenance
[7]	255	67	39	215	-	-	CONTINUATION	Paclitaxel Carbo	Paclitaxel
[9]	206	61	56	150	89	84		Gemcitabine CisP	Gemcitabine
[10]	464	58	39	429	304	90		Gemcitabine CisP	Gemcitabine
[11]	255	61	39	215	-	-		Gemcitabine CarboP	Gemcitabine
[6]	539	61	50	489	470	0		Pemetrexed CisP	Pemetrexed
ESMO 2011	253	60	22	231	225	0		Pemetrexed CisP	Pemetrexed Bev
[5]	181	62	94	87	54	108	SWITCH	Mito Ifo CisP	Vinorelbine
[12]	309	65	51	256	156	54		Gemcitabine CarboP	Docetaxel
[13]	663	60	126	536	328	182		Gem/Doce/Pacli-Plat	Pemetrexed
[17]	173	61	29	144	85	31	BIOTHERAPIES	Plat based chemo	Gefitinib
[15]	889	60	225	664	403	360		Plat based chemo	Erlotinib
[14]	768	64	69	627	606	17		Gem/Doc/Pacli-Plat	Erlotinib Bev
[10]	-	-	-	-	-	-		Gemcitabine CisP	Erlotinib
[8]	296	54	74	221	209	57		Plat based chemo	Gefitinib
Total	5251	61	913	4261	2929	983			

Table 1: Main characteristics of the patients included in the studies eligible for metaanalysis.

For OS, the overall HR relying on 14 sub-studies5-17 amounted to 0.86 (0.80-0.92; p<0.001; fixed effect model), showing a statistically significant reduction of mortality of 14 % in OS (Figures 2-4).

For PFS, the corresponding overall HR relying on 13 sub-studies [5-16] was 0.65 (0.58-0.73; p=0.001; random effect model), meaning a 35 % reduction in risk of disease progression (Figure 3).

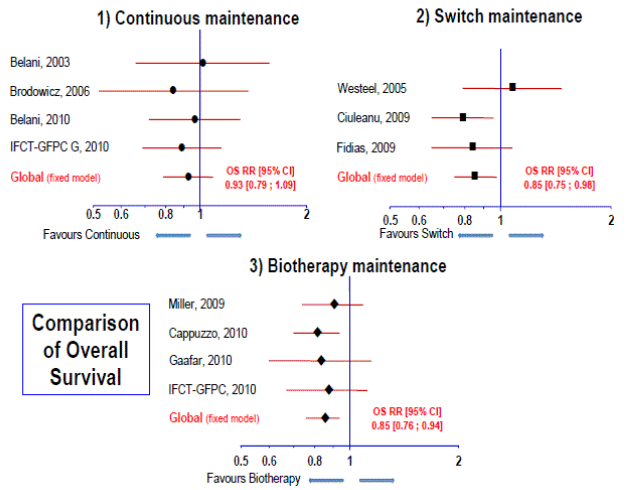

Figure 2: Forest plot of studies with or without maintenance treatment and assessing overall survival.

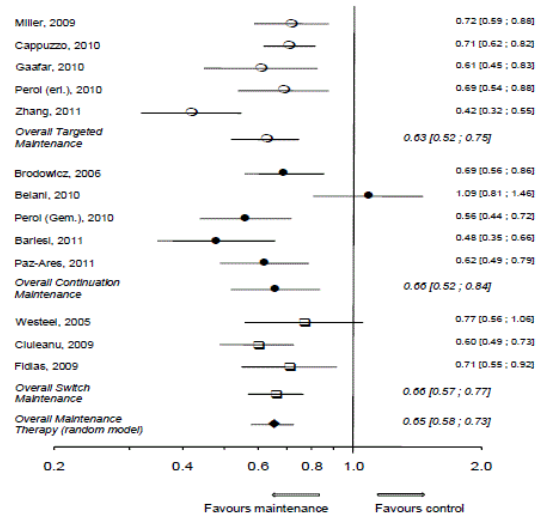

Figure 3: Comparison of progression-free survival between maintenance therapy and placebo or observation.

There was a non-statistically significant improvement in OS for continuation maintenance overall (6 sub-studies; HR 0.89; 0.78-1.03; p=11; fixed effect model) [6,7,9-11,16] but not for gemcitabine only (3 studies; HR 0.91; 0.76-1.09; fixed effect model) [9-11]. There was also a statistically significant improvement in OS for switch maintenance with chemotherapy (3 studies; HR 0.85; 0.75-0.98; p<0.02; fixed effect model) [5,12,13]. Switch maintenance with EGFR TKIs, either erlotinib or gefitinib, also provided a significant OS benefit (5 RCTs, HR 0.85; 0.77-0.93; p=0.001; fixed effect model) [8,10,13-15]. The same results were found when assessing erlotinib only (2 RCTs, HR 0.85; 0.76-0.95) [14,15]. For each study, the HR PFS was plotted against the corresponding difference (in months) in median progression free survival between the group with active maintenance drug and the control group. From the linear regression line thus obtained, we could infer that the difference in overall PFS corresponding to the overall HR PFS of 0.66 was 1.7 month. For OS, there was a poor linear regression fit of the data, making hazardous the calculations.

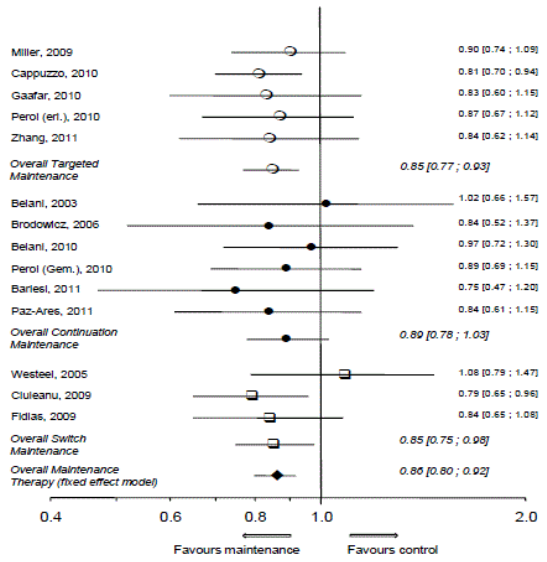

Figure 4: Comparison of overall survival between maintenance therapy and placebo or observation

Considering drug-related toxicities (Figure 5), as expected, all grade haematological side-effects (anaemia, thrombocytopenia, neutropenia) were more frequent with maintenance chemotherapy than in the control group (HRs 4.90, 2.05-11.70; 4.78, 1.20-19; 1.91, 1.28-2.84 respectively). Diarrhoea was also more frequent during maintenance chemotherapy (HR 3.25, 1.93-5.27). Frequencies of fatigue, nausea-vomiting, mucositis and neuropathy were similar in the maintenance group and the control group. As expected, incidence of skin rashes (HR 5.25; 95 % CI 3.06-9.00; p=0.001; random effect model) and diarrhoea (HR 3.88; 95 % CI 2.26-6.69; p=0.001) were higher in the group receiving maintenance therapy with EGFR TKIs than in the control group [2,6,10-12].

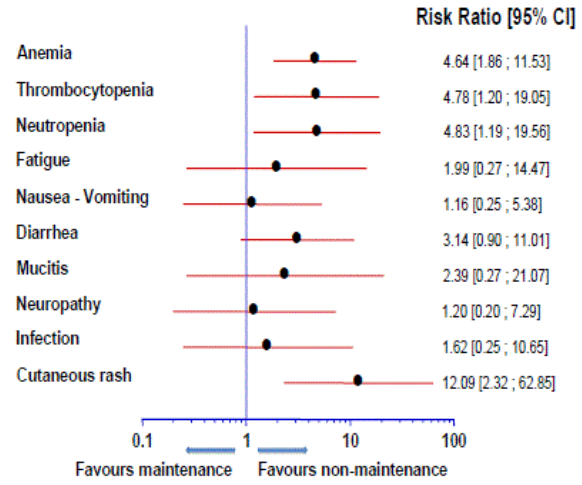

Figure 5: Summary of drug-related toxicities

Discussion

This MA confirms the validity of the concept of maintenance therapy in NSCLC. For OS, the overall HR was 0.85 (0.80-0.91), meaning a 15% reduction in deaths with maintenance therapy. For PFS, the corresponding overall HR was 0.65 (0.58-0.73, random effect model), meaning a decrease by 35% in the risk of progression. These results are far from negligible, considering the poor prognosis of NSCLC and its frequency. However, they represent a rather modest gain in PFS of 1.7 month. At least for PFS, all 13 sub-studies except 2 [5,11] showed a statistically significant difference favouring maintenance, which strengthens the conclusions of the MA. The study by Westeel et al. [5] which found no statistically significant improvement in PFS had included nearly 50% of patients with thoracic radiotherapy. In addition, vinorelbine has no proven efficacy when used as second line therapy. The study by Belani had included many PS2 patients which could have mitigated the results [11]. Conversely, for OS, only the studies by Cappuzzo and Paz Ares showed a statistically significant difference favouring maintenance [6,15]. This discrepancy is probably explained by the lack of statistical power of individual studies when assessing OS, due to the small numbers of patients included in each RCT. This drawback is attenuated by the pooling of studies in this MA.

Overall, both types of maintenance therapy (switch or continuation) significantly improved OS and PFS. These results are in accordance with those of the recent MA published by Zhang et al. **2** which found that switch maintenance but not continuation maintenance substantially improved OS. The MA by Zhang et al. found clinically pertinent and statistically significant improvements in PFS for both continuation and switch maintenance (HRs 0.53, 95% CI 0.43-0.65 and 0.67, 95% CI 0.57-0.78 respectively). However, this concurrent MA included only 8 studies and 3736 patients. More precisely, it did not include the first study by Belani et al. [7] published in 2003 (probably because survival was reported from initiation of induction therapy and

not from maintenance randomisation), the study by Westeel et al. [5] (in which nearly half of patients had induction chemo-radiation), the key PARAMOUNT study by Paz-Ares et al. [6] and, unexpectedly, their own study [8], both presented orally at ASCO meeting 2011 and finally AVAPERL study presented at last ESMO meeting [16]. As indirect comparisons are of questionable value in MAs, we cannot conclude definitely as to the relative benefits of the various types of maintenance (continuation, switch or targeted therapy). The present MA found a significant HR OS for targeted therapies of 0.85 (0.77-0.93). Thus, in the present MA, maintenance with continuation or switch chemotherapies and targeted therapies appeared to provide similar benefits. In PointBreak study, randomized patients to carboplatin, paclitaxel, and bevacizumab followed by bevacizumab maintenance (the ECOG 4599 regimen) *versus* carboplatin-pemetrexed-bevacizumab followed by pemetrexed-bevacizumab maintenance (the PointBreak regimen) [19]; OS was identical between the two arms (13.4 *versus* 12.6 months, HR 1.00, p = 0.95). In PRONOUNCE, a smaller study with a similar approach to PointBreak, enrolled 361 patients and randomized them to carboplatin and pemetrexed followed by maintenance pemetrexed *versus* carboplatin, paclitaxel, and bevacizumab followed by bevacizumab [20]. There were no differences in PFS or OS between the arms. These two studies not only assessed the maintenance but also compared various treatments regimens (induction chemotherapy + maintenance). Consequently they were not included in our MA.

Concerning side-effects, anaemia, thrombocytopenia and neutropenia were significantly more frequent with chemotherapies and skin rashes and diarrhoea more frequent with EGFR TKIs. The large width of 95% CIs for several adverse effects of chemotherapies (nausea-vomiting, mucositis, neuropathy) meant that there were too few events to conclude definitely on the frequency of the corresponding toxicity. Thus, the risks-to-benefit balances of the different types of maintenance therapies (targeted agents, continuation or switch maintenance with chemotherapy) are difficult to assess separately, even in a MA pooling all available RCTs.

When considering each study separately, the median survival benefit provided by maintenance therapy was small (from 0.25 month for the study by Cappuzzo et al. to 3.75 months for the study by Belani in 2003 for OS; from 0.1 month for the study by Belani 2010 to 4 months for the study by Fidias for PFS). According to a recently published statement from Ocana and Tannock, [21] concerning many cancers, a gain in OS should be no less than 3 months, corresponding to a HR of 0.75 and a gain in PFS no less than 4-6 months corresponding to a HR of 0.5 to be clinically meaningful in metastatic solid tumours. These arbitrarily preset HR OS and HR PFS are higher than the corresponding values found in the present MA, confirming the small size of the benefits established by our MA. However, it seems questionable to provide overall data for all types of cancers, with highly variable prognoses. It should be stressed that NSCLC has a poor prognosis.

The main limitation of the present MA was that it was literature-based and not based upon individual patient data, which could allow taking into account the main characteristics of patients (PS, histology, response to induction therapy) when assessing the survival benefit of maintenance therapies. Another limitation is that quality of life was not assessed. Several key issues remain unanswered despite this MA. What is the optimum number of cycles of induction chemotherapy? In non-progressive patients after 2 cycles, a study [22] showed that, compared to 4 cycles of induction chemotherapy, 6 cycles significantly improved PFS (6.2 months for 6 cycles compared with 4.6 months for 4 cycles (HR 0.63; 95% CI 0.50-0.80; p=0.001). Thus, what is the benefit of continuation maintenance compared with 6 cycles of platinum-based chemotherapy? As each RCT did not present separately the results of patients with stable disease or of responders to induction chemotherapy, we could not establish whether patients with stable disease benefited more from switch maintenance whereas responders benefited more from continuation maintenance. Only a MA of individual patient data might provide an answer to this crucial issue. The best way to test this hypothesis would be to perform a prospective randomized trial. In the IFCT-GFPC study assessing gemcitabine as continuation maintenance therapy [10] , the survival benefit was more important among responders (HR 0.44; 95% CI 0.31-0.63) than among patients with stable disease (HR 0.68, 95% CI 0.48-0.97). Conversely, Cappuzzo et al. [15] showed that the survival benefit of erlotinib as switch maintenance compared with placebo after 4 cycles of platinum-based chemotherapy was limited to patients with stable disease (HR 0.72, 95% CI 0.59-0.89, p=0.002), whereas responders did not have any improvement in OS. Finally, the biological and genomic signatures of NSCLC are complex, making it difficult to draw firm conclusions from studies considering all NSCLCs as a single entity. This holds even more true for targeted therapies. More studies should be needed to assess separately the various characteristics of tumours, such as pathological type, especially for targeted therapy.

In conclusion, maintenance therapy whatever its type significantly improved OS and PFS. Switch chemotherapy and EGFR tyrosine-kinase inhibitors appeared to provide similar benefits. Whether clinical and biological tolerance of maintenance therapy is acceptable or not remains to be established.

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