Perspective

Maintenance therapy in advanced non-small cell lung cancer: a prime-time for change?

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Lung cancer is the leading cancer in terms of incidence and mortality in China and its incidence in China is predicted to increase in the next 20 years.[1] The majority of the lung cancer patients are diagnosed with advanced stage disease, for which chemotherapy or targeted therapies are the mainstay palliative treatments. Before the identification of single-driver mutations, like the epidermal growth factor receptor (EGFR) mutation, platinum-based doublet was the standard first line treatment for advanced stage non-small cell lung cancer (NSCLC) patients with a good performance status (PS). However, patient prognosis remains poor and the modest treatment efficacy seems to have reached a plateau despite newer generation of platinum doublets.[2] The recommendation for the duration of first line platinum doublet treatment is 4-6 cycles.[3] The paradigm was based on the fact that a protracted course of chemotherapy did not prolong survival but introduced cumulative toxicities.[4,5] The use of maintenance therapy (MT), defined by Grossi et al[6] as the prolongation of chemotherapy with the administration of additional drugs at the end of a defined number of initial chemotherapy cycles after achieving maximum tumor response, was not considered as a standard option in the past.

With the advent of new cytotoxics and targeted therapies with less cumulative toxicities, the concept of applying MT to prolong survival has been revisited. Two major strategies of MT have been tested, namely switch maintenance therapy and continuation maintenance therapy. Switch maintenance therapy refers to the use of a non-cross-resistant regime immediately after a specified number of cycles of platinum-doublet drugs have rendered stabilization or partial remission of the disease. Theoretically, the non-cross-resistant regime can maximize tumor cell-killing and defer the occurrence of resistant clones. In contrast, continuation maintenance is the continuation of one or more components from the first line regime after achieving a disease-controlling effect by a specified number of chemotherapy cycles. In theory, continuation MT can sustain the anti-proliferative effect of the first line therapy. Both switch and continuation maintenance therapies continue until disease progression (PD) or the occurrence of prohibitive toxicities. The initial phase of platinum doublet is usually referred as "induction" treatment.

Encouraging data on MT bloomed in the past few years and have stirred up debates on the use of MT vs. the conventional "wait and see till progression" paradigm after initial treatment. In this review, current data will be summarized and debates, remaining questions, and the applicability in MT will be discussed.

CONTINUATION MAINTENANCE

Continuation of platinum doublets (Table 1)

A few large randomized control trials (RCT) were conducted to determine the optimal duration of chemotherapy.[4-8] It has been recommended that chemotherapy should be administered for no more than 6 cycles.[9,10] The majority of studies compared short therapy cycles with fixed longer cycles, except the study by Socinski et al[4] which was a true continuation maintenance trial with a platinum doublet as maintenance.

The trial by Socinski randomized patients to receive 4 cycles of paclitaxel and carboplatin or continuation of the same regime until PD or prohibitive toxicities. There were no significant differences in median overall survival (OS), one-year survival and quality of life (QoL) between the two arms. However, more patients experienced grade-2 or higher peripheral neuropathy in the continuation arm. Up to 43% patients suffered ≥grade-2 neuropathy if 8 cycles of treatment were received. Of note, over half of the patients who terminated MT was because of toxicities (16%) or because of the "patients or physicians' choice" (36%), but the exact reasons for termination were not reported. Although this trial showed no added benefits of prolonging platinum doublets, it did not refute the concept of MT. Instead, it highlighted that tolerability and cumulative toxicity are important elements of MT.

Continuation of non-platinum cytotoxics

Since combination chemotherapy resulted in intolerable cumulative toxicity without actual survival advantage,

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Table 1. Summary of trials using chemotherapy as continuation maintenance therapy

Author/Study	Patient number	Induction therapy	Maintenance therapy	Median PFS (months)	Median OS (months)	Most frequent Gr3-4 AEs
Socinski[4] 2002	230	4 × paclitaxel (200 mg/m^2) & carboplatin (AUC 6) q3 wks	Same dose & schedule as induction (n=116)	NR	8.5	Neutropenia 42% ≥Gr 2 Neuropathy 27%
			Observation (n=114)	NR	6.6, P=NS	≥Gr 2 Neuropathy 14%‡
Belani[11] 2003	401	Paclitaxel & carboplatin in 3 different dose schedules for 16 wks	Weekly paclitaxel (70 mg/m^2, 3-week on, 1-week off; n=65)	8.9*	17.5	45% reported ≥1 Gr3-4 AE
			Observation (n=65)	6.8, P=NS	14, P=NS	
Belani[12] 2008	444	4 × carboplatin with weekly paclitaxel	Weekly paclitaxel (70 mg/m^2, 3-week on, 1-week off; n=141)	7.7 (TTP)	9†	Fatigue 2.9% Gr 4 neutropenia 2.1%
		4 × carboplatin with paclitaxel q3week		6.8 (TTP)	10†	Neuropathy 2.1%
Brodowicz[13] (CECOG) 2006	352	4 × gemcitabine (1250 mg/m^2 on D1&8), cisplatin (80 mg/m^2) q3wks	Gemcitabine (1250 mg/m^2 on D1 & 8 q3wks) (n=138)	3.6	10.2	Transfusion 20% Neutropenia 14.9%
			Observation (n=68)	2.0	8.1	Transfusion 6.3%‡
				P <0.001	P=0.195	
Perol[14] 2012	834	4 × gemcitabine (1250 mg/m^2 on D1 & 8), cisplatin (80 mg/m^2) q3week	Gemcitabine (1250 mg/m^2 on D1 &8 q3wks) (n=154)	3.8	12.1	Neutropenia 20.8% Thrombocytopenia 6.5%
			Observation (n=155)	1.9	10.8	
				P <0.001	P=NS	
Belani[15] 2010	519	4 × gemcitabine (1000 mg/m^2 on D1& 8), carboplatin (AUC 5) q3wks (n=472)	Gemcitabine (1000 mg/m^2 on D1 &8 q3wks) (n=128)	3.9	8	Anemia 9.4% Neutropenia 13.3% Thrombocytopenia 9.4%
			Observation (n=127)	3.8	9.3	
				P=NS	P=NS	
Paz-Ares[18,19] 2012 (PARAMOUNT)	939	4 × pemetrexed (500 mg/m^2) & cisplatin (75 mg/m^2) q3wks (n=46)	Pemetrexed (500 mg/m^2 q3wks) (n=359)	4.1	13.9	Neutropenia 4% Anaemia 4%; fatigue 4%
			Placebo (n=180)	2.8	11	Neutopenia 0‡ Anaemia 0.6%‡ Fatigue 0.6%‡
				P <0.0001	P=0.0195	

AE: adverse event; AUC: area under curve; PFS: progression free survival; OS: overall; survival; NR: not reported; NS: not significant statistically; TTP: time to progression; q3wks: every 3 weeks. *Median TTP & OS includes 16 weeks of initial treatment; † Whole group with or without maintenance therapy; ‡P <0.05 between treatment and control. All PFS & OS are calculated from the date of randomization to event unless otherwise specified. Toxicities were either graded by National Cancer Institute Common Terminology Criteria or World Health Organization Criteria.

studies were then conducted to investigate whether single agent MT might be beneficial.

Paclitaxel

Two studies by Belani's group tested the dose schedules of paclitaxel in combination with carboplatin, with a secondary purpose to investigate the feasibility of MT using weekly paclitaxel.[11,12] This MT appeared to have a longer progression free survival (PFS) and OS and was generally well tolerated. Unfortunately the studies were either underpowered or lacked a control arm and no definitive conclusion about the role of MT could be made.

Gemcitabine

Three trials using maintenance gemcitabine therapy have been reported. The Central European Cooperative Oncology Group (CECOG) compared gemcitabine to observation after induction therapy with gemcitabine and cisplatin.[13] There was a significant delay (1.6 months) in time-to-progression (TTP) in the MT group, but without OS benefits. No deterioration in the QoL as measured by the Lung Cancer Symptom Scale was noted in the gemcitabine MT patients. The major toxicity was myelosuppression, notably 20% required transfusions, but no febrile neutropenia was recorded in the maintenance phase.

Another recently published trial from the French group showed a similar observation.[14] It investigated whether continuation MT with gemcitabine or switch MT with erlotinib would yield a better survival compared to observation after 4 cycles of gemcitabine-cisplatin. Patients with PD would receive predefined pemetrexed to avoid bias in the OS analysis. Superior PFS but not OS was observed in the MT arm. Interestingly, both the CECOG and the French trials demonstrated that the PFS and OS benefit predominated in patients with good PS. In contrast, Belani et al[15] failed to demonstrate any OS or PFS benefit using maintenance gemcitabine with a similar study design. The high proportion of patients with a fair PS (64%) in Belani's study and a much lower percentage receiving post-study therapy (16% vs. 57%–74% in the CECOG and French studies) may account for the difference. Considering the observations in these three trials, PS may be an important indicator for selecting patients who would benefit from MT.[16]

Pemetrexed

Pemetrexed is a novel multi-targeted antifolate. After the landmark trial by Scagliotti et al,[17] it has become one of the standard options in first line chemotherapy for advanced non-squamous NSCLC. Given its favorable toxicity profile, convenient administration (a 10-minute infusion every 21 days) and single agent efficacy, pemetrexed was tested as a maintenance agent for both switch and continuation maintenance therapy. PARAMOUNT was a double blinded phase III RCT testing the efficacy of continuation pemetrexed in non-squamous NSCLC patients without PD receiving 4 cycles of induction pemetrexed and cisplatin.[18,19] The primary endpoint was PFS, and it was also powered for OS analysis. The final OS data was recently presented in the Annual Meeting of American Society of Clinical Oncology (ASCO) in 2012. Maintenance pemetrexed

showed a positive impact on both PFS (*HR* 0.62; *P* <0.0001) and OS (*HR* 0.78; *P*=0.0195). The proportion of patients receiving post-discontinuation therapy was similar in both groups. Only 5% of patients discontinued treatment due to drug-related toxicity. Expectedly, more drug related toxicities (neutropenia, anemia and fatigue) were recorded in the MT arm but the incidence of overall grade 3–4 drug induced side effects were below 10%. QoL measured by the EuroQol 5-dimensional scale (EQ-5D) was similar in both groups. Overall, the 2.9-month OS improvement with limited toxicities is encouraging.

Continuation of targeted therapy

Bevacizumab is a monoclonal antibody targeting the vascular endothelial growth factor (VEGF). It is indicated for treatment of advanced non-squamous NSCLC in combination with platinum doublets. Two large randomized trials, ECOG4599 and AVAiL, demonstrated improvement in treatment outcomes; a 2-month OS improvement in E4599 but only modest PFS, and no OS benefit in AVAiL.[20,21] In these two studies, patients were assigned to six cycles of platinum-based chemotherapy or platinum-based chemotherapy plus bevacizumab. Bevacizumab was continued as MT until PD. Whether the continuation of bevacizumab beyond 6 cycles was really required in order to prolong survival remains unknown. Interestingly, in a retrospective analysis of NSCLC patients treated with platinum doublets and bevacizumab in 17 community oncology clinics in the US, only 27% continued bevacizumab MT.[22] Reasons for discontinuing bevacizumab included lack of response in the induction phase (15%), switching to another therapy (11%), toxicity (11%), poor PS (6%), and patient refusal (5%).

Cetuximab, a monoclonal antibody targeting the EGFR, was shown to improve OS by 1.2 months when it was added to vinorelbine and cisplatin doublets in patients with advanced EGFR-expressing NSCLC.[23] Cetuximab was also continued until PD. Similar to results from the AVAIL and E4599 trials, when chemotherapy was the control arm a true benefit of cetuximab in the maintenance phase was not conclusively shown. Currently, cetuximab is not approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of advanced NSCLC.

Given the high treatment cost, potentially severe toxicities (like hemorrhage and thromboembolism), lack of single agent activity and reliable predictive biomarkers, the use of monoclonal antibodies alone as MT should be carefully discussed with patients. Further clinical trials addressing their role as MT are needed.

Continuation of cytoxics together with targeted therapy (Table 2)

Combination of bevacizumab with chemotherapy as maintenance agents was also evaluated. Patel et al[24] reported a phase II study using 6-cycles of pemetrexed, carboplatin and bevacizumab followed by maintenance with pemetrexed and bevacizumab (coined as Patel's regime) until progression. The response rate was 55%, and median PFS and OS were 7.8 and 14.1 months respectively. Toxicity was acceptable.

Following this favorable preliminary result, an ongoing phase III trial (AVAPERL1) is being conducted to compare maintenance bevacizumab with bevacizumab plus pemetrexed after induction with bevacizumab, cisplatin and pemetrexed.[25] The results were presented at the European Multidisciplinary Cancer Congress in 2011. The combination maintenance approach demonstrated a 50% reduction in risk of PD compared to single bevacizumab maintenance (PFS 10.2 vs. 6.6 months), without jeopardizing the QoL.[26] The OS data have not yet matured. The safety profile was comparable to that of regimens indicated for the use of bevacizumab.

Another interesting trial, POINTBREAK, which had been

Table 2. Summary of trials using combination of targeted therapy and cytotoxics as continuation maintenance therapy

Author/ Study	Patient number	Induction therapy	Maintenance therapy	Median PFS (months)	Median OS (months)	Most frequent Gr3-4 AEs during maintenance
Patel[24] 2009	50	6 × Pemetrexed (500 mg/m^2), carboplatin (AUC 6) & Bv (15 mg/kg) q3wks	Pemetrexed (500 mg/m^2) & Bv (15 mg/kg) q3wks	7.8	14.1	Thrombocytopenia2% Arterial thrombosis 2% Protienuria 2%
Barlesi[25-26] 2012 (AVAPERL1)	376	4 × Pemetrexed (500 mg/m^2), cisplatin (75 mg/m^2) & Bv (7.5 mg/kg) q3wks	Pemetrexed (500 mg/m^2) & Bv (7.5 mg/kg) q3wks (*n*=128)	10.2	NR	43% reported ≥1 Gr3-4 AE
			Bv (7.5 mg/kg) q3wks (*n*=125)	6.6 *P* ≤0.001	15.7	35% reported ≥1 Gr3-4 AE
Patel [27] 2012 (POINTBREAK)	939	4 × Pemetrexed (500 mg/m^2), carboplatin (AUC 6) & Bv (15 mg/kg) q3wks	Pemetrexed (500 mg/m^2) & Bv (15 mg/kg) q3wks (*n*=292)	6.0	12.6	Anaemia 14.5%*† Thrombocytopenia 23.3%*† Neutropenia 25.8% *† Fatigue 10.9%*† Neuropathy 0%*† Alopecia (Gr1/2) 6.6%*†
		4 × Paclitaxel (200 mg/m^2), carboplatin (AUC 6) & Bv (15 mg/kg) q3wks	Bv (15 mg/kg) q3wks (*n*=298)	5.6 *P*=0.012	13.4 *P*=NS	Anaemia 2.7% Thrombocytopenia 5.6% Neutropenia 40.6% Fatigue 5%; Neuropathy 4.1% Alopecia (Gr1/2) 36.8%*†

Bv: Bevacizumab; NR: Not reached. All PFS & OS are calculated from the date of randomization to event unless otherwise specified. Toxicities were graded by National Cancer Institute Common Terminology Criteria. *Toxicity during the whole course of treatment; †*P* <0.05 between treatment and control.

just presented at the Chicago Multidisciplinary Symposium in Thoracic Oncology 2012, compared the E4599 regimen with the Patel's regimen.[27,28] The primary endpoint of OS was not met (*HR* 1.0; *P*=0.95) and PFS was only slightly superior in Patel's regimen (*HR* 0.83; *P*=0.012). However, of note, the randomization was performed before induction treatment and only 63% of patients without PD could enter the maintenance phase. Pre-specified exploratory analysis for patients receiving MT, was an OS of 17.7 months and a PFS of 8.6 months (Patel's regimen) vs. 15.7 and 6.9 months (E4599 regime). With regards to the toxicity profile, no clear superiority can be demonstrated for either regimen. Whether the maintenance portion of Patel's regime was better or not remained unanswered, although exploratory analysis did suggest its superiority. The exploratory analysis supported the findings of the AVAPERL trial, that the PFS was better in combination MT compared to bevacizumab alone.

SWITCH MAINTENANCE AND SEQUENTIAL THERAPY

Switch maintenance refers to the delivery of a non-cross resistant agent immediately after the initial stabilization of disease by a first line regime. Goldie and Coldman[29] suggests that even small lesions possess drug resistant clones which proliferate over time, so early switch to a non-cross resistant agent can theoretically eradicate more tumor cells before resistance occurs.

Switch maintenance using cytotoxics

There are a few large phase III RCTs exploring the role of switch maintenance in advanced NSCLC after induction chemotherapy (Table 3). One older trial used a platinum triplet as induction therapy, which is not considered as standard treatment nowadays. Westeel et al[30] investigated vinorelbine alone after induction mitomycin, ifosfamide and cisplatin (MIC). Responders were randomized to vinorelbine or observation. No significant PFS and OS differences were detected. Special attention should be paid to the fact that 32% of patients discontinued maintenance on vinorelbine due to prohibitive toxicities or patient refusal. Leucopenia and infection were frequent in the MT arm. This again highlighted that tolerability should be a prerequisite of an agent whem being tested as MT.

Two newer trials, however, demonstrated clinical benefits in patients receiving switch MT. Docetaxel is a standard second line agent for treating advanced NSCLC patients with progression after platinum doublet therapy. Fidias et al[31] assessed the efficacy of switching to docetaxel immediately vs. delayed docetaxel administration upon PD after carboplatin-gemcitabine. This was an important trial to address whether sequential therapy made a difference compared to a traditional watch-and-wait policy. A significant improvement in PFS and a trend towards OS improvement (study powered to detect a 4-month OS difference) in favor of immediate treatment were observed. A noteworthy point was that only 63% of patients randomized to the delayed treatment arm actually received second line therapy. Many patients had a significant decline in their PS by the time they had PD, rendering them unsuitable for chemotherapy. Those who received delayed docetaxel actually showed a comparable OS (12.5 months) to the immediate switch group. Thus, the benefit could be attributed to a greater proportion of patients being exposed to additional therapy.

Another phase III RCT by Ciuleanu et al[32] randomized patients who did not progress after four cycles of platinum-based chemotherapy, to receive either pemetrexed or placebo until PD. Benefits in PFS and OS were seen in the maintenance arm, *HR* 0.6 and *HR* 0.79, respectively (P <0.05). The treatment was well tolerated and only 5% discontinued treatment due to toxicity. Most common toxicities were fatigue, neutropenia, and anemia. Comparable to the trial of Fidias, 67% patients in the placebo group got second-line therapy. However, among those who received further treatment, only 18% received pemetrexed. This trial led to the approval of pemetrexed as a switch maintenance agent by both the EMA and FDA.

Switch maintenance using targeted therapy (Table 4)

SATURN was the first study to demonstrate that an EGFR-tyrosine kinase inhibitor (TKI) delivered as switch maintenance therapy after platinum doublets could improve

Table 3. Summary of trials using cytotoxics in switch maintenance treatment

Author/Study	Patient number	Induction therapy	Maintenance therapy	Median PFS (months)	Median OS (months)	Most frequent Gr3-4 AEs during maintenance
Westeel[30] 2005 (GCOT)	573	Mitomycin C 6 mg/m^2 D1 Ifosfamide 1.5 g/m^2 D1-3 Cisplatin 30 mg/m^2 D1-3 q4wks × 2–4 cycles	Vinorelbine 25 mg/m^2 weekly (max 6 months) (*n*=91)	5.0	12.3	Leucopenia 45.9% Infection 12.6%; Anaemia 9.1% Neuropathy 7.4%
			Observation (*n*=90)	3.0, *P*=NS	12.3, *P*=NS	
Fidias[31] 2009	566	Gemcitabine (1000 mg/m^2) D1&8, carboplatin (AUC 5) q3wks × 4 cycles	Docetaxel 75 mg/m^2 (max 6 cycles) q3wks (*n*=153)	5.7	12.3	Fatigue 9.7% Neutropenia 27.6% Diarrhoea 0.7%
			Delayed docetaxel 75 mg/m^2 q3wks upon PD, (*n*=156)	2.7 *P* <0.001	9.7 *P*=0.085	Fatigue 4.1% Neutropenia 28.6% Diarrhoea 5.1%
Ciuleanu[32] 2009 (JMEN)	663	4 cycles platinum-based doublets	Pemetrexed 500 mg/m^2 q3wks (*n*=441)	4.0	13.4	Fatigue 5%; Anaemia 3% Neutropenia 3%
			placebo (*n*=222)	2.0 *P* <0.001	10.6 *P*=0.012	Fatigue, anaemia & neutropenia all <1%*

AUC: Area under curve. *P <0.05 between treatment and control. All PFS & OS are calculated from the date of randomization to event unless otherwise specified. Toxicities were either graded by National Cancer Institute Common Terminology Criteria.

PFS and OS, irrespective of the EGFR status.[33] However, the survival benefits were modest in the intention-to-treat population. As expected, the most striking PFS benefit was in patients bearing activating EGFR mutations (*HR* 0.10, *P* <0.0001), but this did not translate into the same magnitude of OS benefit due to cross-over effect. The treatment was well tolerated. Only 12% of patients experienced ≥grade-3 toxicity. Skin rash was the most common toxicity (9%). Five percent terminated the treatment due to toxicity.

Another French study investigated whether switch maintenance with erlotinib or continuation with gemcitabine after four cycles of gemcitabine and cisplatin could improve PFS.[14] The continuation part has been discussed in the previous section. Maintenance erlotinib resulted in improved PFS (*HR* 0.69; *P*=0.03), but not in OS. The study was, however, not powered to assess OS differences. The incidence of ≥grade-3 adverse effects was low (16%), which was about half of that in the maintenance gemcitabine arm (28%), but the incidence of severe adverse event was similar to gemcitabine.

Three trials were performed to assess the efficacy of gefitinib, another EGFR TKI, in the switch maintenance setting.[34-36] Two were performed in Asian populations (Chinese and Japanese) and the other was conducted in Europe. The European trial was stopped prematurely due to slow accrual.[35] All demonstrated modest improvement in PFS but no OS benefits. EGFR mutational status was not a mandatory requirement at the start of these trials. In the Chinese INFORM trial, around 27% of the studied population was available for EGFR mutation testing. Similar to SATURN, the greatest clinical benefits were seen in the group with activating EGFR mutations (PFS *HR* 0.17, 0.07–0.42). In the population with unknown mutational status, quite a remarkable risk reduction (60%) was also observed. This was likely related to the relatively high incidence of EGFR mutations in the Chinese population. In a recently reported large scale molecular epidemiological study on the EGFR mutational status in an Asian population, 50.2% of the Chinese population harbored EGFR mutations.[37] The difference in frequency of EGFR mutation in different populations could have affected the benefits derived from TKI switch maintenance.

The majority of these trials were designed before the identification of the EGFR mutation as a reliable predictive biomarker for EGFR TKI treatment. The clinical scenario is now different in this genomic-based treatment era. Nowadays, EGFR mutations should be determined in all patients with metastatic disease whenever possible, and those with activating mutations should receive upfront TKI. In the EGFR wild type population, it is still unknown whether maintenance pemetrexed, erlotinib, or combined chemotherapy with bevacizumab is the best maintenance agent.

Switch maintenance using combined targeted therapy

Combination of erlotinib and bevacizumab had previously been studied in the preclinical setting and as second line therapy for recurrent NSCLC.[38,39] Such combinations were also tested in the switch MT setting.[40] ATLAS was a phase III RCT comparing maintenance bevacizumab and erlotinib with bevacizumab alone after induction therapy with platinum-doublet plus bevacizumab. Modest PFS was observed but without OS improvement. No unexpected toxicity was noted.

RESULTS OF META-ANALYSIS

A few meta-analyses (MA) were recently published to elucidate the role of continuation and switch maintenance therapy.[41-43] Some of the reported trials were either

Table 4. Summary of trials using targeted therapy in switch maintenance treatment

Author/Study	Patient number	Induction therapy	Maintenance therapy	Median PFS (months)	Median OS (months)	Most frequent Grade 3–4 AEs during maintenance
Cappuzzo[33] 2010 (SATURN)	1949	4 cycles platinum-based doublets	Erlotinib 150 mg daily (*n*=438)	12.3 weeks	12	Rash 9% Diarrhoea 2%
			Placebo (*n*=451)	2.75, *P* <0.001	11, *P*=0.0088	Rash & Diarrhoea 0
Perol[14] 2012	834	4 × gemcitabine (1250 mg/m^2 on D1 & 8), cisplatin (80 mg/m^2) q3wks	Erlotinib 150 mg daily (*n*=155)	2.9	11.4	Rash 9% Pneumonia 2.6% Infection 2.6%
			Observation (*n*=155)	1.9, *P*=0.003	10.8, *P*=NS	
Zhang[34] 2012 (INFORM)	298	4 cycles platinum-based doublets	Gefitnib 250 mg daily (*n*=148)	4.8	18.7	Raised ALT 2%
			Placebo (*n*=148)	2.6, *P* <0.0001	16.9, *P*=NS	
Takeda[36] 2010 (WJTOG)	604	4 × Platinum doublets	Gefitnib 250 mg daily (*n*=298)	4.6	13.7	Anaemia 13.4%*† Raised ALT 10.7%*†
		6 × Platinum doublets	Placebo (*n*=300)	4.3, *P* <0.001	12.9, *P*=0.11	Anaemia 21.8% Raised ALT 4%
Gaafar[35] 2011 (EORTC)	173	4 cycles platinum-based doublets	Gefitnib 250 mg daily (*n*=86)	4.1	10.9	Raised ALT 10.6%‡ Diarrhoea 1.2%
			Placebo (*n*=87)	2.9, *P*=0.0015	9.4, *P*=NS	Raised ALT 1.2%
Kabbinavar[40] (ATLAS) 2010	1160	4 cycles platinum-based doublets + Bv 15 mg/kg q3wks	Erlotinib 150 mg daily Bv 15 mg/kg q3wks (*n*=370)	4.8	15.9	Rash 10.4%‡ Diarrhoea 9.3%
			Bv 15 mg/kg q3wks & placebo (*n*=373)	3.8, *P*=NS	13.9, *P*=NS	Rash & Diarrhoea <1%

ALT: Alanine transferase. All PFS & OS are calculated from the date of randomization to event unless otherwise specified. Toxicities were graded by National Cancer Institute Common Terminology Criteria. *Toxicity during the whole course of treatment; †*P* <0.05 between treatment and control; ‡ Descriptive statistics only.

terminated prematurely or not powered to detect OS differences, and meta-analyses can help identify the true magnitude of benefits. The three MA by Behara et al, Zhang et al and Yuan et al[41-43] had similar conclusions, that single agent MT improved PFS and OS, at the expense of increased toxicities. In addition, the switch maintenance approach appeared to have a better OS benefit compared to continuation therapy.

Although MA helped summarizing these results into simpler conclusions, a few caveats on these findings should be noted. First, the result of PARAMOUNT (pemetrexed continuation maintenance) was not included in these three MA, since the OS data had just been recently published. This large scale trial reporting increased OS would influence the overall OS benefit observed in continuation maintenance therapy patients. Second, the proportion of patients receiving second-line therapy and the agents they received varied in each arms in different studies and this would interfere with the interpretation of OS benefits. Third, none of these MA were based on individual patient data. Last, the variation in induction schemes, EGFR mutational status, frequency and modalities of response assessment all complicate the analysis of the overall outcomes.

QUESTIONS UNRESOLVED

The paradigm of MT had gradually gained acceptance as one of the standard options.[10,44] Although data on new agents bloomed in the past few years, a lot of questions still remained to be unraveled.

Study endpoints

The best study endpoint is always debatable. OS is the most reliable and convincing endpoint. However, lung cancer treatment is increasing in complexity and subsequent therapy can affect OS. Trials using OS as an endpoint are more time consuming, more expensive and are prone to dilution factors like cross-over effects and exposure to different subsequent lines of therapy. PFS is thus a suitable endpoint to avoid the dilution effect. However, PFS differs in definition across trials and is affected by the frequency of imaging and assessment. PFS may not be a reliable surrogate for OS or for QoL, which are probably more important from the patient's perspective. Some newer trials use PFS without grade-4 toxicity as the endpoint, which can take into account the potential toxicity inflicted on patients during MT.

Optimal agent and strategy

Both maintenance strategies are supported by RCTs. There is no direct comparison between the two maintenance strategies. Some data suggest the response during induction therapy can shed light in the following MT. In the SATURN trial, preplanned subgroup analysis showed patients achieving stable disease (SD) after first line treatment derived a more pronounced benefit in OS with erlotinib than those who achieved a complete or partial response (CR/PR). In contrast, in the PARAMOUNT trial (continuation pemetrexed), after induction therapy the PFS benefit was more pronounced in patients with CR/PR than in those with SD, but the difference was no longer seen in the subsequently released OS data. It seems logical that a "switch" is needed when only SD is achieved in the first line treatment while the initial component that achieve PR/CR can be "continued" until it becomes refractory. Further validation is needed.

Predictive biomarkers would be valuable to identify the subgroup which benefits most in MT: Like in the SATURN and INFORM trial where patients with EGFR mutations derived the greatest survival benefits. The expressions of thymidylate synthase and RRM1 have been suggested to affect the efficacy of pemetrexed and gemcitabine respectively. These kinds of biomarkers may help to identify the most suitable maintenance agent when prospective data is available.

Up till now, there are no data to show which maintenance agent is the best. The ongoing ECOG5508 trial will be of interest for comparing the maintenance components; bevacizumab, pemetrexed and its combination after the induction part of the E4599 regime. Another onging ERACLE trial focuses on the QoL outcome comparing patients receiving the PARAMOUNT regime with the E4599 regime.[45]

Cost effectiveness analysis

Erlotinib, pemetrexed and bevacizumab are currently approved for MT. However these are expensive agents and the derived PFS and OS benefits are modest. The exact magnitude of the benefit from a bevacizumab maintenance phase is not yet defined in the E4599 trial. Cost-effectiveness analysis is needed to compare this new treatment with the conventional "watch and wait" policy. It is even more important when expensive combination targeted therapy are tested as new maintenance agents. This information is needed for clinicians and policy makers to justify the new treatment protocols.

INCORPORATING CURRENT DATA INTO DAILY PRACTICE

Lung cancer therapy is no longer a "one-size-fit-all" regime; histological subtypes and molecular profiles are important determinants to decide the optimal first line treatment for NSCLC patients, which in turn affects the choice of MT. The new data from combined agents for MT, and whether these agents are affordable across different health care systems, further complicates the choice of the MT.

It should be stressed that the majority of the trials were only conducted in patients with good PS (PS 0 or 1). It is not certain whether the same benefits can be seen in PS 2 patients, and it would be advisable not to administer MT

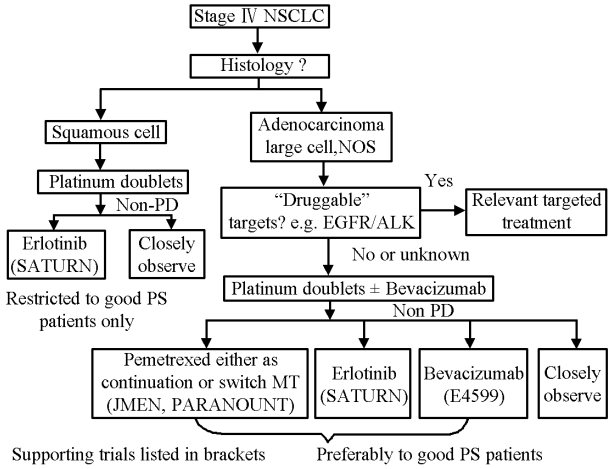

Figure 1. Simplified decisional algorithm for maintenance therapy in metastatic non-small cell lung cancer. Second line therapy not included.

in this group of patients unless it is performed within the context of clinical trials.

The proposed decisional algorithm according to current evidence is shown in Figure 1. Combined chemotherapy and targeted therapy is not included in Figure 1 because whether combination MT fares better than single agent chemotherapy is still unknown. Although bevacizumab is included as a choice, it should be emphasized that the OS benefit was only seen in the E4599 but not the AVAIL trial, and its *in vivo* single agent activity remains questionable.

The identification of reliable predictive biomarkers would be ideal to select patients who can derive maximum benefits from MT.

CONCLUSION

Is it the prime time for changing the paradigm to maintenance treatment? Given the three large scale RCTs with both positive impact in PFS and OS, MT should be one of the standard options, but not the sole option. Watch and wait until progression is still a valid option, especially when the disease burden is small and the risk of rapid life threatening progression is low. The decision on MT should be a joint decision by patients and doctors. The different maintenance strategies, magnitude of benefits, added toxicities, and the risk of rapid PD during drug holidays should be thoroughly discussed. Any decline in the patient's PS and any residual toxicity from induction therapy should be carefully assessed. After all, the most important determinant is the patient's preference, which should always be respected. If a patient prefers a drug holiday, a timely interval assessment should be made before the patient's condition declines to a state beyond allowing second line therapy.

REFERENCES

1. Chang S, Dai M, Ren JS, Chen YH, Guo LW. Estimates and prediction on incidence, mortality and prevalence of lung cancer in China in 2008. Chin J Epidemiol 2012; 33: 391-394.
2. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92-98.
3. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004; 22: 330-353.
4. Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, et al. Phase III trial comparing a defined duration of therapy vs. continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 2002; 20: 1335-1343.
5. Smith IE, O'Brien ME, Talbot DC, Nicolson MC, Mansi JL, Hickish TF, et al. Duration of chemotherapy in advanced nonsmall-cell lung cancer: a randomized trial of three vs. six courses of mitomycin, vinblastine, and cisplatin. J Clin Oncol 2001; 19: 1336-1343.
6. Grossi F, Aita M, Follador A, Defferrari C, Brianti A, Sinaccio G, et al. Sequential, alternating, and maintenance/ consolidation chemotherapy in advanced non-small cell lung cancer: a review of the literature. Oncologist 2007; 12: 451-464.
7. von Plessen C, Bergman B, Andresen O, Bremnes RM, Sundstrom S, Gilleryd M, et al: Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. Br J Cancer 2006; 95: 966-973.
8. Park JO, Kim SW, Ahn JS, Suh C, Lee JS, Jang JS, et al. Phase III trial of two vs. four additional cycles in patients who are nonprogressive after two cycles of platinum based chemotherapy in non-small-cell lung cancer. J Clin Oncol 2007; 25: 5233-5239.
9. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009; 27: 127-145.
10. Felip E, Gridelli C, Baas P, Rosell R, Stahel R, Panel Members. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. Ann Oncol 2011; 22: 1507-1519.
11. Belani CP, Barstis J, Perry MC, La Rocca RV, Nattam SR, Rinaldi D, et al. Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. J Clin Oncol 2003; 21: 2933-2939.
12. Belani CP, Ramalingam S, Perry MC, LaRocca RV, Rinaldi D, Gable PS, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin vs. standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008; 26: 468-473.
13. Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006; 52: 155-163.
14. Pérol M, Chouaid C, Pérol D, Barlési F, Gervais R, Westeel

V, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy vs. observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012; 30: 3516-3524.

15. Belani CP, Waterhouse DM, Ghazal H, Ramalingam SS, Bordoni R, Greenberg R, et al. Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) vs. BSC, following standard combination therapy with gemcitabine-carboplatin (G-Cb) for patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2010; 28 (Suppl): 15s (abstr 7506).
16. Custodio A, de Castro J. Strategies for maintenance therapy in advanced non-small cell lung cancer: current status, unanswered questions and future directions. Crit Rev Oncol Hematol 2012; 82: 338-360.
17. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced stage non-small-cell lung cancer. J Clin Oncol 2008; 26: 3543-3551.
18. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care vs. placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012; 13: 247-255.
19. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed plus best supportive care vs. placebo plus best supportive care immediately following induction treatment with pemetrexed plus cisplatin for advanced nonsquamous NSCLC. J Clin Oncol 2012; 30 (Suppl): LBA 7507
20. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355: 2542-2550.
21. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010; 21: 1804-1809.
22. Dranitsaris G, Beegle N, Ravelo A, Kalberer T, Yu E, Thomas S. Evaluating the Impact of Bevacizumab Maintenance Therapy on Overall Survival in Advanced Non-Small-Cell Lung Cancer. Clin Lung Cancer 2012; Epub ahead of print.
23. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009; 373: 1525-1531.
24. Patel JD, Hensing TA, Rademaker A, Hart EM, Blum MG, Milton DT, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009; 27: 3284-3289.
25. Barlesi F, de Castro J, Dvornichenko V, Kim JH, Pazzola A, Rittmeyer A, et al. AVAPERL (MO22089): final efficacy outcomes for patients (pts) with advanced non-squamous non-small cell lung cancer (nsNSCLC) randomised to continuation maintenance (mtc) with bevacizumab (bev) or Bev + pemetrexed (pern) after first-line (1L) Bev-cisplatin (cis)-pem treatment (Tx). EUR J CANCER 2011; 47: 16.
26. Barlesi F, Scherpereel A, Gervais R, Gorbunova VA, Vikström A, Ahn M, et al. AVAPERL1 (MO22089): Maintenance (mtc) bevacizumab (bev) with or without pemetrexed (pem) in patients (pts) with advanced nonsquamous non-small cell lung cancer (nsNSCLC) treated with first-line (1L) bev-cisplatin (cis)-pem: Interim safety data. J Clin Oncol 2011; 29 (Suppl): abstr 7562.
27. Patel J, Socinski MA, Garon EB, Reynolds CH, Spigel DR, Hermann RC, et al. A randomized, open-label, phase 3, superiority study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (B) followed by maintenance Pem+B vs. paclitaxel (Pac)+Cb+B followed by maintenance B in patients (pts) with stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC); J Thorac Oncol 2012; 7 (Suppl): S336-S338.
28. Patel JD, Bonomi P, Socinski MA, Govindan R, Hong S, Obasaju C, et al. Treatment rationale and study design for the pointbreak study: a randomized, open-label phase III study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab vs. paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. Clin Lung Cancer 2009; 10: 252-256.
29. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979; 63: 1727-1733.
30. Westeel V, Quoix E, Moro-Sibilot D, Mercier M, Breton JL, Debieuvre D, et al. Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. J Natl Cancer Inst 2005; 97: 499-506.
31. Fidias PM, Dakhil SR, Lyss AP, Loesch DM, Waterhouse DM, Bromund JL, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009; 27: 591-598.
32. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care vs. placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 374: 1432-1440.
33. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010; 11: 521-529.
34. Zhang L, Ma S, Song X, Han B, Cheng Y, Huang C, et al. Gefitinib vs. placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomized phase 3 trial. Lancet Oncol 2012; 13: 466-475.
35. Gaafar RM, Surmont VF, Scagliotti GV, Van Klaveren RJ, Papamichael D, Welch JJ, et al. A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP01/03). Eur J Cancer 2011; 47: 2331-2340.
36. Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, et al.

Randomized phase III trial of platinum-doublet chemotherapy followed by gefi tinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a West Japan Thoracic Oncology Group Trial (WJTOG0203). J Clin Oncol 2010; 28: 753-760.

37. Yang PC, Shi Y, Au JS, Srinivasan S, Cornelio GH, Tsai CM, et al. Molecular epidemiological prospective study of EGFR mutations from Asian patients (pts) with advanced lung adenocarcinoma (PIONEER). J Clin Oncol 2012; 15 (suppl): abstr 1534.
38. Herbst RS, Johnson DH, Mininberg E, Carbone DP, Henderson T, Kim ES, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. J Clin Oncol 2005; 23: 2544-2555.
39. Herbst RS, Ansari R, Bustin F, Flynn P, Hart L, Otterson GA, et al. Efficacy of bevacizumab plus erlotinib vs erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line CT (BeTa): a double-blind, placebo controlled, phase 3 trial. Lancet 2011; 377: 1845-1854.
40. Kabbinavar FF, Miller VA, Johnson BE, O'Connor PG, Soh C. ATLAS Investigators. Overall survival (OS) in ATLAS, a phase IIIB trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). J Clin Oncol 2010; 28 (Suppl): 15s (abstr 7526).
41. Behera M, Owonikoko TK, Chen Z, Kono SA, Khuri FR, Belani CP, et al. Single agent maintenance therapy for advanced stage non-small cell lung cancer: a meta-analysis. Lung Cancer 2012; 77: 331-338.
42. Zhang X, Zang J, Xu J, Bai C, Qin Y, Liu K, et al. Maintenance therapy with continuous or switch strategy in advanced non-small cell lung cancer: a systematic review and meta-analysis. Chest 2011; 140: 117-126.
43. Yuan DM, Wei SZ, Lü YL, Zhang Y, Miao XH, Zhan P, et al. Single-agent maintenance therapy in non-small cell lung cancer: a systematic review and meta-analysis. Chin Med J 2012; 125: 3143-3149.
44. Azzoli CG, Temin S, Aliff T, Baker S Jr, Brahmer J, Johnson DH, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol 2011; 29: 3825-3831.
45. Galetta D, Pisconti S, Cinieri S, Pappagallo GL, Gebbia V, Borsellino N, et al. Induction pemetrexed and cisplatin followed by maintenance pemetrexed vs. carboplatin plus paclitaxel plus bevacizumab followed by maintenance bevacizumab: a quality of life-oriented randomized phase III study in patients with advanced non-squamous non-small-cell lung cancer (ERACLE). Clin Lung Cancer 2011; 12: 402-406.

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