Impact of Targeted Therapy on the Survival of Patients With Advanced-Stage Non-small Cell Lung Cancer in Oncosalud - AUNA

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Abstract

Background: Lung cancer is still a prevalent and fatal neoplasm in developing countries. In the last decades, chemotherapy (CHT) maintenance occupied an important role in the treatment, as well as targeted therapies. We aimed to evaluate the survival impact of targeted therapy in advanced lung cancer at a private Peruvian institution (Oncosalud - AUNA).

Methods: We reviewed retrospectively medical records of patients with advanced-stage non-small cell lung cancer (NSCLS) (clinical stage III-IV) who received CHT and maintenance treatment with target therapy (TT) or CHT. The impact was assessed by progression-free survival (PFS) and overall survival (OS) using the Kaplan–Meier method, and comparisons of survival curves were performed using log-rank or Breslow test and Cox model.

Results: The median age of the patients was 65 years. Clinical characteristics, as well as the treatment type, showed no significant difference between the two groups. The maintenance schedule in those receiving CHT was generally pemetrexed (70%) and in those receiving TT was erlotinib (60.7%). In patients receiving TT, the median PFS was 13 months compared to 7 months in those receiving CHT; likewise, the median OS was 45 and 17 months, respectively. The PFS and OS curves showed significant differences ($P < .05$), achieving a better survival in subjects treated with TT.

Conclusion: Progression-Free Survival and OS were superior in patients who received targeted therapy than those treated only with CHT, the 2 years rate of PFS and OS was nearly double to those who received only CHT-based treatments.

Introduction

Lung cancer represents one of the public health problems in many regions of the world; it remains as the most frequent neoplasms and the main cause of death from cancer worldwide.[1] It represents approximately 12% of all malignant neoplasms, with an incidence rate of 22.5 and a mortality rate of 18.6 per 100 000 persons.[2] In Peru, it corresponds to approximately 4.8% of all malignant neoplasms and is the second leading cause of death from cancer; reaching an incidence rate of 9.1 and a mortality rate of 8.0 per 100 000 persons.[3]

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Lung cancer is a heterogeneous disease. Most cases belongs to non-small cell lung cancer (NSCLC) subtype, characterized by a poor prognosis, due to their aggressiveness and that most patients are diagnosed at advanced-stage disease.[1]

On the other hand, the standard treatment for patients with advanced disease (III-IV stages) is still a platinum-based doublet in most developing countries. However, a poor response is usually achieved with a short progression time of 4–6 months, a median overall survival (OS) between 8–10 months, and a 2 years OS rate between 10–15%.[4,5]

The use of platinum-based doublets has been subject of research and controversy for decades, achieving a modest survival.[6] However, with the incorporation of anti-angiogenic and tyrosine kinase inhibitors (TKIs), it has been possible to relatively improve patient survival; although, there is a controversy between the findings reported by controlled clinical trials and the results of real-world clinical practice.[7]

Even though early diagnosis represents a great challenge in these patients, advances in the molecular biology of lung cancer have made it possible to identify genes related to better prognosis, such as the epidermal growth factor receptor (EGFR), the kinase of anaplastic lymphoma (ALK), or the c-ros oncogene 1 (ROS1) proto-oncogene, among others that are susceptible to targeted therapies.[8]

As a result of the identification of these genes, drugs have been designed to target these genetic alterations (mutations or rearrangements). These drugs are called targeted therapy, and are incorporated into the standard treatment for NSCLC; however, their application within the clinical practice as standard treatment is still limited due to its high cost.[9]

This study evaluates the effect of maintenance with TKI or (bevacizumab) on the survival of patients with advanced-stage NSCLC who received systemic chemotherapy (CHT) with platinum-based doublets as standard of care in a private specialized institution in the management of cancer patients (Oncosalud - AUNA).

Patients and Methods

A retrospective study was carried out to evaluate the effect of maintenance treatment with target therapy (TT) in patients with advanced-stage NSCLC who received platinum-based doublets (cisplatin or carboplatin) in Oncosalud - AUNA between 2008–2013.

To evaluate the impact of TT on survival, two groups of patients were considered: the reference group (Group 1: CHT) and the study group (Group 2: Targeted therapy). Group 1 was composed of patients with advanced NSCLC who achieved some response to CHT treatment and who received conventional maintenance treatment (another CHT regimen, mCHT) during the study period. Group 2 was composed of patients with advanced NSCLC who achieved some response to treatment with CHT and who received maintenance treatment

with targeted therapy (bevacizumab, crizotinib, erlotinib, afatinib, cetuximab, or gefitinib) during the study period. Our primary endpoints were OS and progression-free survival (PFS).

The clinical, pathological, and treatment characteristics as well as follow-up data were collected from the electronic medical records. The data collected were as follows: age at diagnosis, sex, ECOG scale, clinical stage, date of diagnosis, histological diagnosis, treatment, first-line CHT schedule, CHT start date, number of cycles of CHT, clinical response, maintenance treatment, recurrence or progression date, date of death, or last contact.

The clinical characteristics and treatment were reported using numerical summary statistics (median, range, and frequencies). The clinical characteristics between the treatment groups were compared using the Chi-square test or Fisher's exact test.

Overall survival was defined as the time between the date of diagnosis and the date of death or date of last follow-up, and PFS as the time between the date of response and the date of progression (death) or last control date. The survival (PFS and OS) was determined using the Kaplan–Meier method and described using survival curves. The median follow-up was calculated using the inverse of the Kaplan–Meier method. Comparisons of survival curves according to clinical, pathological, and treatment were performed using the log-rank or Breslow tests, when required. The Cox model was used for multivariate analysis. All evaluations were performed at a significance level of 5%.

The data were analyzed and processed using the SPSS version 26 software.

Results

A total of 58 patients with advanced-stage NSCLC were included in the study, thirty of them had received platinum-based duplets followed by a maintenance regimen (Group 1) and the remaining 28 received platinum-based doublets followed by either bevacizumab or erlotinib (Group 2).

Patient's Characteristics

The age of the patients ranges from 35 to 85 years of age, reaching a median of 65 years of age in both treatment groups. The characteristics of patients in Group 1 and Grupo 2 were 76.7% and 78.6% of patients were older than 60 years, 53.3% and 39.3% were female, 16.7% and 14.3% had an ECOG scale greater than 1, and 63.3% and 71.4% were diagnosed at stage IV, respectively. The distribution of patients by age groups, sex, ECOG scale, and clinical stage did not show significant differences ($P > .05$). The histological type was adenocarcinoma, in 86.7% and 92.9% of the patients, respectively; which did not differ significantly ($P = .439$). The histological grade and neither the EGFR status were not determined in most of the cases. (Table 1)

Table 1. Clinical Characteristics of Patients with Advanced-Stage Non-Small Cell Lung Cancer.

Characteristic	Chemotherapy[a] (n = 30)	Targeted therapy[b] (n = 28)	P-value
Age at diagnosis (years)			
Median (range)	65 (44, 77)	65 (35, 85)	.862
>60	7 (23.3)	6 (21.4)	
<60	23 (76.7)	22 (78.6)	
Sex			
Female	14 (46.7)	17 (60.7)	.284
Male	16 (53.3)	11 (39.3)	
ECOG scale			
0–1	25 (83.3)	24 (85.7)	.802
2–4	5 (16.7)	4 (14.3)	
Clinical stage			
III	11 (36.7)	8 (28.6)	.583
IV	19 (63.3)	20 (71.4)	
Histology type			
Adenocarcinoma	26 (86.7)	26 (92.9)	.439
Others	4 (13.3)	2 (7.1)	

[a]Platinum-based doublets.
[b]Targeted therapy as a maintenance treatment.

Table 2. Treatment Modality of Patients with Advanced-Stage Non-Small Cell Lung Cancer.

Characteristics	Chemotherapy[a] (n = 30)	Targeted therapy[b] (n = 28)	
First-line chemotherapy			
Carboplatin plus:			.464*
PEM	16 (53.3)	5 (17.9)	
GEM	6 (20.0)	7 (25.0)	
PTX	5 (16.7)	11 (39.3)	
Cisplatin plus:			
PEM	2 (6.7)	3 (10.7)	
GEM	1 (3.3)	2 (7.1)	
Chemotherapy cycles			.311
4–5	10 (33.3)	6 (21.4)	
6+	20 (66.7)	22 (78.6)	
According scheme: 4–5cys**			
CBP+PEM	5 (31.2)	1 (20.0)	
CBP+GEM:	4 (66.7)	2 (28.6)	
CBP+PTX	1 (20.0)	1 (9.1)	
Clinical response			.412
Complete	3 (10.0)	2 (7.1)	
Partial	12 (40.0)	15 (53.6)	
Stable	15 (50.0)	11 (39.3)	
Maintenance therapy			NA
Pemetrexed	21 (70.0)	—	
Others CHT	9 (30.0)	—	
Bevacizumab	—	15 (53.6)	
Erlotinib	—	13 (46.4)	

[a]Platinum-based doublets, [b]targeted therapy as a maintenance treatment
*CBP + others vs CDDP + others: P = .464.
**The other patients received 6+ cycles. NA: no applied.

Table 3. PFS and SO of Patients with Advanced-Stage Non-Small Cell Lung Cancer Who Received Chemotherapy or Targeted Therapy.

Characteristic	Chemotherapy[a] (n = 30)	Targeted therapy[b] (n = 28)	*P*-value
Status			
Alive	8 (26.7)	13 (46.4)	.118
Dead	22 (73.3)	15 (53.6)	
Follow-up (years)			
Median (95%CI)	3.6 (3.3, 4.0)	4.1 (3.6, 4.5)	NA
Progression-free survival (PFS)			
Median (95%CI)	7.2 (5.8, 8.5)	13.1 (8.1, 19.0)	.008
Rate at 1-year	24.3	55.9	
Rate at 2-years	17.4	29.8	
Overall survival **(OS)**			
Median (95%CI)	17.2 (13.2, 21.1)	45.0 (22.7, 67.2)	.014
Rate at 1-year	75.4	85.7	
Rate at 2-years	39.2	67.9	

[a]Platinum-based doublets.
[b]Targeted therapy as a maintenance treatment. NA: Not applied.

Cancer Treatment

The platinum-based doublets that received were carboplatin (CBP) plus pemetrexed (PEM), gemcitabine (GEM) or paclitaxel (PTX), and cisplatin (CDDP) plus PEM or GEM; although, the majority received carboplatin-based (90% and 82.2% of the patients in Group 1 and 2, respectively, P = .464). In group 1, 53.3% of the patients received CBP + PEM, 20% CBP + GEM, and 16.7% CBP + PTX. In group 2, 39.3% received CBP + PTX, 25% CBP + GEM, and 17.9% CBP + PEM. The remaining patients received other platinum-based doublets. Regarding the number of treatment cycles, 33.3% and 21.4% of the patients received 4 to 5 cycles, and 66.7% and 78.6% of the remaining received 6 or more cycles of CHT, without significant difference between both groups (P = .311). 50 and 60.7% of the patients achieved measurable response to treatment in each group, respectively; the remainder had stable disease, which did not differ significantly between both groups (P = .412). (Table 2)

Maintenance Treatment

In group 1, 70% of the patients received maintenance with PEM and the remaining other CHT regimens. In group 2, 53.6% received bevacizumab concomitant to the platinum-based doublets and 46.4% received erlotinib. No patients in group 1 received treatment after standard treatment (CHT + mCHT) or before disease recurrence or progression; while 60% of the patients in group 2 received some treatment after targeted therapy of before recurrence or disease progression. **(**Table 2**)**

Progression and Status

In total, 86.7% in group 1 and 85.7% in group 2 developed disease progression, without significantly differences between both groups (P = .499). Also, 80.8% and 87.5% of subjects with

disease progression received a new CHT regimen, and a relatively large group (14.3% and 19.0%) underwent a subsequent treatment with TKI. At the evaluation period, only 26.7% and 46.4% of the patients were alive, while 73.3% and 53.6% of the patients died due to disease progression. The median follow-up of patients in group 1 was 3.6 years (95% CI: 3.3–4.0) and 4.1 years (95% CI: 3.6–4.5) in group 2. **(**Table 3**)**

Progression-Free Survival and Overall Survival

The median PFS was 7.2 months (95% CI: 5.8–8.5) in group 1, and 13.1 months (95% CI: 8.1–18.0) in group 2. The PFS rate at 1 and 2 years were 24.3% and 17.4% in group 1, and 55.9% and 29.8% in group 2; being relatively better in those who received targeted therapy (group 2) and poor in those who received standard treatment (group 1) (P = .008). (Table 3 and Figure 1).

The median OS was 1.4 years (95% CI: 1.1–1.7) in group 1, and 3.7 years (95% CI: 1.9–5.5) in group 2. Besides, the OS rate at 1 and 2 years were 75.4% and 39.2% in group 1, and 85.7% and 67.9% in group 2. Finally, OS was greater among patients treated with targeted therapy (group 2) and dismal in those who received standard treatment (group 1) (P = .014). (Table3 and Figure 2)

Target Therapy Effect Adjusted for Clinical Characteristics

In the multivariate analysis, TT reduced the risk of disease progression by more than 50% (HR: .47; 95% CI: .3–.8) in subjects with advanced-stage NSCLC. Moreover, the metastatic status is a crucial factor for PFS in this group of patients (HR: 2.1; 95% CI: 1.1–4.2). On the other hand, treatment with TT reduce the risk of death from the cancer by more than 60% (HR: .36; 95% CI: .2–.7) in subjects with advanced-stage NSCLC. Additionally, the age remains an important factor for survival in patients with advanced-stage NSCLC. (Table 4)
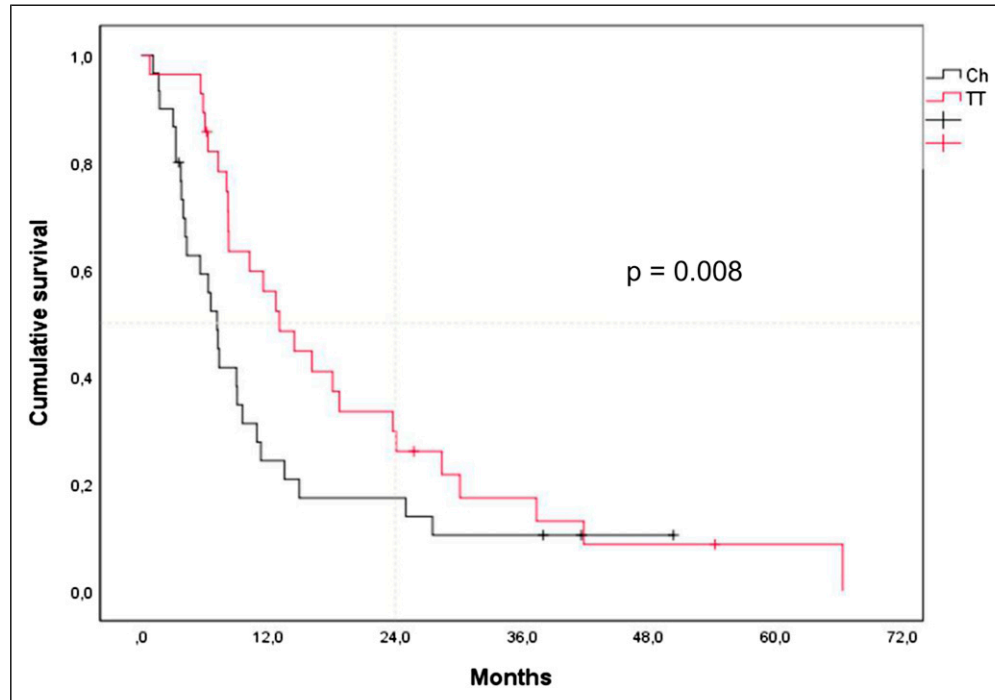
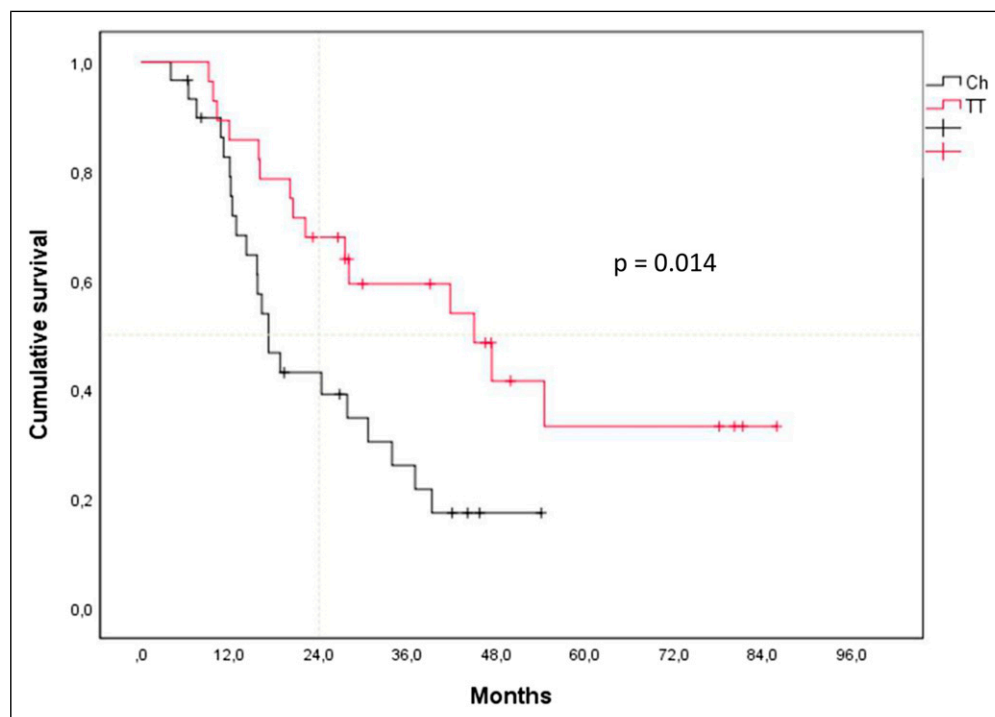**Figure 1.** PFS according to type of maintenance therapy.

Figure 2. OS according to type of maintenance therapy.

Table 4. Adjusted Effect of Targeted Therapy on PFS and OS of Patients with Advanced-Stage Non-Small Cell Lung Cancer.

	PFS HR (95%CI)	P	OS HR (95%CI)	P
Targeted therapy				
No	Reference	.013	—	.005
Yes	.47 (.26, .85)		.36 (.18, .74)	
Age (years)				
<60	Reference	.027	—	.008
>60	.41 (.19, .90)		.30 (.12, .73)	
Sex				
Female	Reference	.096	—	.290
Male	.59 (.31, 1.10)		.68 (.34, 1.38)	
ECOG scale				
0–1	Reference	.179	—	.430
2+	.55 (.23, 1.32)		.65 (.22, 1.89)	
Clinical stage				
III	Reference	.034	—	.341
IV	2.12 (1.1, 4.25)		1.48 (.66, 3.35)	

HR: Hazard Ratio, PFS: Progression-free survival, OS: Overall Survival.

Discussion

The discovery of a large amount of genomic and proteomic data, gene expression, and mutation over a decade ago has made possible to identify and classify NSCLC into molecularly distinct subgroups and to design treatment strategies based on the identification of specific driver mutations such as EGFR, Kirsten rat sarcoma (KRAS), HER2, V-raf murine sarcoma viral oncogene homolog B1 (BRAF), ALK, and PIK3CA[10] Erlotinib and Gefitinib are drugs available as targeted therapies for EGFR mutations, and crizotinib, an ALK inhibitor, has shown efficacy in ALK fusion lung cancer.[11] Moreover, the determination of genetic alterations in non-smoking patients with lung adenocarcinoma is the current strategy to choose the best therapy.

A total of 58 patients with advanced-stage NSCLC were included in the study, of which 30 had received platinum-based duplets plus a maintenance regimen (Group 1) and the remaining 28 received platinum-based duplets plus bevacizumab or erlotinib as maintenance (Group 2), without significant difference about the clinical characteristics. This study showed a significant improvement in terms of survival for patients receiving TT. Specifically, patients who received CHT-TT (bevacizumab or erlotinib) had better survival, which was comparable with the information presented by Bruce E. Jhonson et al.[12] In their study, it was shown that CHT-bevacizumab plus erlotinib significantly improved the survival of patients. Likewise, in the study by Martin Reck et al,,[13] it was evidenced that the addition of bevacizumab to CHT achieved better survival.

The favorable OS in our study for group 2 can be related to TT. Yusuke Takagi et al.[14] reported that bevacizumab represents an important factor in the prognosis of patients with NSCLC; also, Kazuhisa Nakasama et al.[15] demonstrated that CHT with cisplatin plus pemetrexed improves OS in patients who were eligible for bevacizumab as maintenance therapy. These studies support that the eligibility of bevacizumab represents a favorable prognosis according to the findings of our study.

In our study, we present an improvement in the NSCLC management based on TT in a limited-source setting. This premise is supported by the study by Ryan Gentzler et al.[16] who showed that for patients with NSCLC treated with carboplatin and paclitaxel, bevacizumab should be added, and maintenance of bevacizumab is the logical option. Although maintenance regimens were shown to improve survival, the bevacizumab regimen is named the most expensive, according to the study by Gayarthri Kumar et al.[17] Therefore, the benefits in survival overweight the financial toxicity for these type of patients.

A study carried out by the Lung Cancer Mutation Consortium[18] reported the results of molecular tests carried out in 1007 patients with lung adenocarcinoma from 14 centers between 2009 and 2012, finding a significant improvement in the survival of patients who received targeted therapy compared to those who do not. A remarkable difference with the study of this group is that they adopted different tests including mass spectrometry, Sanger type sequencing, and multiplex hotspot panels, also focusing on a panel of 10 drivers including EGFR mutation, KRAS, ALK rearrangements, and other alterations.

Other studies that we take as references are those of the Eastern Cooperative Oncology Group (ECOG), ECOG 4599, and AVAiL[19-21] in which the addition of bevacizumab to the standard first-line CHT carboplatin and paclitaxel resulted in a significant progression of survival, and it was continued in those patients who responded to 4 or 6 cycles of the aforementioned combination.

In ECOG 4599,[19] the addition of bevacizumab (15 mg/kg) to carboplatin-paclitaxel produced a significant and clinically relevant improvement in OS, which was the primary endpoint of the study (12.3 months vs 10.3 months, HR .79; *P* = .003). Furthermore, those patients who received bevacizumab showed a significant improvement in objective response and PFS. It was also noted that bevacizumab treatment was well tolerated by the patients but was associated with a significant increase in the risk of bleeding (4.4% vs .7%, p0.001).

A systematic review and meta-analysis of phase II/III studies[22] concluded that the addition of bevacizumab to platinum-based CHT as first-line treatment in patients with advanced NSCLC significantly prolonged OS and PFS, even more in patients with adenocarcinoma, unlike the other histologies, without unexpected toxicities.

In the AVAiL study,[20] the addition of bevacizumab (at doses of 7.5 and 15 mg/kg) to cisplatin gemcitabine produced small improvements in PFS but no difference in OS. Two other large observational studies, SAIL and ARIES,[23] confirmed the safety profile of first-line bevacizumab associated with a wide variety of CHT regimens; however, its efficacy in combination with other regimens is still unknown. In our study, the median OS was 1.4 (95% CI: 1.1–1.7) years in group 1, and in group 2 it was 3.7 (95% CI: 1.9–5.5) years; reaching an OS rate at 1

and 2 years of 75.4% and 39.2% in group 1, and in group 2 of 85.7% and 67.9%, which present a significant difference between both groups (P = .004).

A relevant question about the sequence treatment arises at the end of standard CHT, whether or not to continue maintenance with bevacizumab. In this sense, our study has observed cases that received the different ways of trying to prolong PFS, thus receiving maintenance therapy with pemetrexed in 70% of the patients in Group 1, and targeted therapy with bevacizumab in 53.6% and erlotinib in 46.4% of Group 2 patients. On the other hand, 60.7% of our patients received some type of post-therapy, these being pemetrexed, pemetrexed-bevacizumab, bevacizumab, and erlotinib from Group 2.

The AvaALL study[24] was the first phase III study to evaluate bevacizumab in multiple lines of treatment beyond disease progression. The investigators randomly assigned 485 patients with non-squamous NSCLC to receive bevacizumab plus standard CHT or standard CHT alone. Patients have initially been treated with double platinum-based CHT and at least two cycles of bevacizumab. The results showed that although OS was longer in patients who received bevacizumab plus standard CHT, it was not significantly longer compared to those in the standard CHT alone arm (11.9 vs 10.2 months; hazard ratio [HR], .84; 90% CI, .71–1.00; P = .104). In the AvaALL study,[24] in the bevacizumab plus standard CHT arm compared to the standard CHT alone arm (76.5% vs 60.3%), the most frequent adverse events (AEs) were fatigue, asthenia, diarrhea, nausea, anemia, and dyspnea. On the other hand, thromboembolism, hypertension, and proteinuria were also more frequent in those who received bevacizumab and standard CHT (48.6% vs 27.2%)

Therefore, our study is only a proof of concept that individuals who receive treatment according to the "driver" mutations found, as well as anti-angiogenic biological drugs, live longer than those who do not, a finding that has been more recently confirmed by other randomized trials to determine whether molecular evidence-based targeted therapy extends survival.

Currently, there are other options such as immunotherapy for the treatment of advanced NSCLC. Targeted therapy with anti-vascular endothelial growth factor receptor (VEGFR) antibodies (aflibercept and ramucirumab) and TKIs with anti-VEGFR selectivity (sorafenib, sunitinib, nintedanib, cediranib, motesanib, pazopanib, axitinib, and vandetanib) have shown response and improved PFS but no advantages in OS of patients with advanced NSCLC.[25] Therefore, the established standard of bevacizumab in combination with carboplatin-paclitaxel in the first line, and ramucirumab in combination with docetaxel in the second line are recommended in recent guidelines.

Furthermore, substantial progress has resulted from targeted immunotherapy with either programmed death-ligand 1 (PD-L1) or programmed death (PD-1) in patients with NSCLC. Thus, based on new data from clinical trials, immunotherapy constitute a new standard in the second line of treatment (nivolumab and pembrolizumab), or first-line treatment (pembrolizumab) independently from PD-L1 expression.[26]

The combination of immunotherapies including bevacizumab can enhance the immune system's ability to kill cancer. The current and future role of first-line biological therapies for NSCLC includes the combination with erlotinib and bevacizumab in populations with EGFR mutations as well as the combination therapy with atezolizumab and bevacizumab.

Conclusion

In patients with advanced-stage NSCLC with some response to first-line treatment with platinum-based doublets CHT, maintenance treatment with targeted therapy relatively improves the survival of patients compared to those who received additional courses or other maintenance CHT regimens. The median and 2-years survival rates of PFS and OS in patients who received targeted therapy were nearly double that obtained in patients who received CHT regimens. Finally, targeted therapy reduces the risk of recurrence or progression, as well as the risk of mortality in more than 50% of patients than in those who received CHT regimens as a maintenance treatment.

Authors Contribution

AA, LM., DE., CV. RG. and CJF. extracted data; AA, LM., DE., CV. RG. and CJF. designed the research, analyzed results and wrote the paper.

Declaration of Conflicting Interests

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E386.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin*. 2018;68:394-424.

3. Ferlay J, Colombet M, Soerjomataram I, et al. Global and regional estimates of incidence and mortality for 38 cancers: Globocan 2018. *Int J Cancer*. 2018;144:1941-1953.

4. SEER. *SEER Cancer Statistics Review 1975-2016*. [Internet]. SEER. cited December 2, 2019.Available from: https://seer.cancer.gov/csr/1975_2016/index.html

5. Nasim F, Sabath BF, Eapen GA. Lung cancer. *Med Clin*. 2019;103(3):463-473.

6. Baxevanos P, Mountzios G. Novel chemotherapy regimens for advanced lung cancer: Have we reached a plateau? *Ann Transl Med*. 2018;6(8):139.

7. Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer*. 2019;18(1):60.

8. Johnson BE, Kris MG, Berry LD, et al. A multicenter effort to identify driver mutations and employ targeted therapy in patients with lung adenocarcinomas: The lung cancer mutation consortium (LCMC). *J Clin Oncol*. 2013;31(15_suppl l):8019.

9. Zhu N, Dong C, Weng S, Yuan Y, Yuan Y. A patient of advanced NSCLC with a new EGFR Exon 19 insertion mutation and its response to EGFR-TKIs. *JCPSP*. 2019;29 :S126-S128.

10. Giudice G, Petsalaki E. Proteomics and phosphoproteomics in precision medicine: Applications and challenges. *Briefings Bioinf*. 2019;20(3):767-777.

11. Scagliotti G, Stahel RA, Rosell R, Thatcher N, Soria J-C. ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development. *Eur J Cancer*. 2012;48:961-973.

12. Johnson BE, Kabbinavar F, Fehrenbacher L, et al. ATLAS: Randomized, double-blind, placebo-controlled, phase iiib trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31(31):3926-3934.

13. Lima ABC, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non small cell lung cancer: A systematic review and meta-analysis. *PLoS One*. 2011;6(8):e22681.

14. Takagi Y, Toriihara A, Nakahara Y, et al. Eligibility for bevacizumab as an independent prognostic factor for patients with advanced non-squamous non-small cell lung cancer: A retrospective cohort study. *PLoS One*. 2013;8(3):e59700.

15. Nakashima K, Murakami H, Omori S, et al. Doublet chemotherapy with cisplatin and pemetrexed is associated with a favorable outcome in patients with advanced non-squamous non-small-cell lung cancer who are eligible for bevacizumab and maintenance therapy. *Mol Clin Oncol*. 2016;5(5):575-578.

16. Gentzler RD, Patel JD. Maintenance treatment after induction therapy in non-small cell lung cancer: Latest evidence and clinical implications. *TAM*. 2014;6(1):4-15.

17. Kumar G, Woods B, Hess LM, et al. Cost-effectiveness of first-line induction and maintenance treatment sequences in nonsquamous non-small cell lung cancer (NSCLC) in the U.S. *Lung Cancer*. 2015;89:294-300.

18. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006.

19. Lopez-Chavez A, Young T, Fages S, et al. Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the eastern cooperative oncology group 4599 study: Results of an exploratory analysis. *J Thorac Oncol*. 2012;7(11):1707-1712.

20. Reck M, von Pawel J, Zatloukal P, 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(9):1804-1809.

21. Russo AE, Priolo D, Antonelli G, Libra M, Mccubrey JA, Ferraù F. Bevacizumab in the treatment of NSCLC: Patient selection and perspectives. *Lung Cancer Targets Ther*. 2017;8:259-269.

22. Soria J-C, Mauguen A, Reck M, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2013;24(1):20-30.

23. Sandomenico C, Costanzo R, Carillio G, et al. Bevacizumab in non-small cell lung cancer: Development, current status and issues. *Curr Med Chem*. 2012;19(7):961-971.

24. Gridelli C, Bennouna J, de Castro J, et al. Randomized phase IIIb trial evaluating the continuation of bevacizumab beyond disease progression in patients with advanced non-squamous non-small-cell lung cancer after first-line treatment with bevacizumab plus platinum-based chemotherapy: Treatment rationale and protocol dynamics of the AvaALL (MO22097) trial. *Clin Lung Cancer*. 2011;12(6):407-411.

25. Lammers PE, Horn L. Targeting angiogenesis in advanced non-small cell lung cancer. *J Natl Compr Cancer Netw*. 2013;11(10):1235-1247.

26. Gong J, Chehrazi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: A comprehensive review of registration trials and future considerations. *JITC*. 2018;6:8.