Barw Medical Journal | 2024;2(3):57-64
Journal home page: https://barw.krd/index.php/BMJ

Systematic Review

Effect of Sunitinib in the Management of Lung Cancer: A Systematic Review of Clinical Trials

Rebaz M. Ali[1], Sami S. Omar[2], Fahmi H. kakamad[3]*, Harem K. Ahmed[4], Diyar A. Omar[5], Yousif M. Mahmood[4], Mohammed Q. Mustafa[6], Aland S. Abdullah[3], Marwan N. Hassan[7], Dahat A. Hussein[4], Suhaib H. Kakamad[8], Hiwa O. Abdullah[4], Hawbash M. Rahim[9], Berun A. Abdalla[10], Shvan H. Mohammed[11]

1. *Hiwa Cancer Hospital, Sulaimani Directorate of Health, Sulaymaniyah, Kurdistan, Iraq*
2. *Rizgary Oncology Center, Peshawa Qazi Street, Erbil, Kurdistan, Iraq*
3. *College of Medicine, University of Sulaimani, Madam Mitterrand Street, Sulaymaniyah, Kurdistan, Iraq*
4. *Smart Health Tower, Madam Mitterrand Street, Sulaymaniyah, Kurdistan, Iraq*
5. *Medical Laboratory Technology, Shaqlawa Technical College, Erbil Polytechnic University, Erbil, Kurdistan, Iraq*
6. *Department of Medical Analysis, Tishk International University, Erbil, Kurdistan, Iraq*
7. *Kscien Organization for Scientific Research (Middle East Office), Hamid Street, Azadi Mall, Sulaymaniyah, Kurdistan, Iraq*
8. *Collage of Medicine, Department of Immunology and Hematology, Kurdistan University of Medical Science, Sanandaj, Iran*
9. *Department of Medical Laboratory Science, College of Health Sciences, University of Human Development, Kurdistan Region, Sulaymaniyah, Iraq*
10. *Department of Biology, College of Education, University of Sulaimani, Madam Mitterrand Street, Sulaymaniyah, Kurdistan, Iraq*
11. *Xzmat Polyclinic, Rizgari, Kalar, Sulaymaniyah, Kurdistan, Iraq*

* ***Corresponding author***: *fahmi.hussein@univsul.edu.iq (F.H. Kakamad). Doctor City, Building 11, Apartment 50, Zip code: 46001, Sulaymaniyah, Kurdistan, Iraq*

Keywords:
Small-cell lung cancer
Sunitinib
Erlotinib
Targeted therapy

Received: April 25, 2024
Revised: May 31, 2024
Accepted: June 25, 2024
First Published: June 29, 2024

Citation: Ali RM, Omar SS, Kakamad FH, Ahmed HK, Omar DA, Mahmood YM, et al. Effect of Sunitinib in the Management of Lung Cancer: A Systematic Review of Clinical Trials. Barw Medical Journal. 2024;2(3):57-64. https://doi.org/10.58742/bmj.v2i2.95

Abstract

Introduction

Lung cancer is the most common cancer in terms of both incidence and mortality. Although usually managed with surgery, novel immunotherapies are gradually becoming more popular. The effect of sunitinib with and without erlotinib in the management of lung cancer is reviewed.

Methods

Eligible search engines and databases were screened to identify studies published in English. Any randomized clinical trials studying the effect of sunitinib, either alone or in combination with erlotinib, were included.

Results

Thirteen studies with a total sample size of 1,062 cases were included. Males (59.5%) were more common than females (40.5%), and the average age of patients was 64 ± 5.03. Most of the patients (71.5%) had a positive smoking status, and non-small cell carcinoma was the most common lung cancer type (95.4%). Almost all of the adverse events, such as headache (100%), weight loss (100%), constipation (100%), leukocytopenia (96%), pain (92.3%), hypertension (90%), dyspnea (88.7%), cough (84.3%), fatigue (81.6%), fever/chills (77.3%), thrombocytopenia (75%), nausea (73.8%), neutropenia (72%), anorexia (71.4%), vomiting (65.1%), anemia (61.3%), and diarrhea (54.5%) were more common in the sunitinib-only group. The mean overall survival for patients receiving sunitinib alone was 213 days, whereas, for patients receiving sunitinib combined with erlotinib, it was 270 days.

Conclusion

Adverse events may be encountered more frequently in treatment with sunitinib alone compared to the combination of sunitinib and erlotinib. However, sunitinib alone may result in higher disease stability and lower disease progression. Nevertheless, combination therapy may yield a longer median overall survival.

1. Introduction

Lung cancer refers to malignant tumors originating from the parenchyma of the lung [1]. Globally, the disease is the most common type of cancer in terms of both incidence and mortality. This cancer is responsible for approximately two million diagnoses and 1.8 million mortalities each year [2]. Similar to other forms of cancer, there seems to be a positive correlation between lung cancer and increasing age [3]. The incidence of lung cancer is generally 69 per 100,000 individuals; however, this number increases to 751 per 100,000 in men above the age of 75 [4]. Due to the rise in its occurrence, the disease is among the most frequently studied types of cancer [5]. Although many etiologies have been linked with the disease, cigarette smoking is the most common risk factor by far [6]. Small-cell carcinoma and non-small-cell carcinoma make up the two main types of lung cancer, with the latter occurring more frequently [7]. The cancer is generally at an advanced stage by the time of presentation. Symptoms include cough, the most prevalent, followed by hemoptysis and chest pain. The main treatment approach, especially reserved for the early stages of the disease, is surgery [6]. Recently, targeted therapies such as erlotinib as an epidermal growth factor (EGFR) inhibitor, durvalumab as a PD-L1 inhibitor, and pembrolizumab as a PD-1 inhibitor are all among the relatively therapeutic agents that can be used in different forms of lung cancer [8-10]. These agents are beneficial for advanced stages of cancer, especially those with specific mutations that can be targeted since surgery alone is not sufficient to eradicate the tumor [8-10]. This study reviewed the effect of sunitinib, a multi-targeted receptor tyrosine kinase inhibitor, with and without erlotinib in managing lung cancer.

2. Methods

2.1. Study design

All clinical trials with patients receiving sunitinib alone or combined with erlotinib were systematically reviewed. This study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.

2.2. Data sources and search strategy

The Google Scholar, CINAHL, PubMed/MEDLINE, Cochrane Library, Web of Science, and EMBASE were all thoroughly screened. The (sunitinib OR Sutent) AND (“lung cancer" OR "lung cancers" OR "lung carcinoma" OR "lung carcinomas" OR "pulmonary cancer" OR "pulmonary carcinoma" OR "bronchogenic cancer" OR " bronchogenic carcinoma" OR "bronchial cancer" OR "bronchial carcinoma") keywords were used in the search.

2.3. Eligibility Criteria

This study included any randomized clinical trial investigating the efficacy of sunitinib alone or in combination with erlotinib for lung cancer. The selected studies should have clearly provided data specific to the type of tumor, its management, and the outcomes of management. To maintain the study's validity, any study published in predatory journals was excluded [11].

2.4. Study selection process

Two researchers screened the studies' titles and abstracts to select those that met the eligibility criteria. A third researcher was recruited to help settle disagreements between the initial two researchers.

2.5. Data items

The data collected included author name, publication year, phase of the clinical trial, sample size, gender, median age, smoking status, performance status, type and histology of lung cancer, number of previous treatment therapies, type, dose, and duration of therapy, adverse events, and outcomes of each therapeutic group.

2.6. Data analysis and synthesis

A Microsoft Excel (2019) workbook sheet was used to collect the data, followed by a descriptive analysis on Statistical Package for Social Sciences (SPSS) 26.0 software. The data were presented as mean, standard deviation, frequency, and percentage.

3. Results

3.1 Study Selection

The initial systematic search found 69 papers. Of these, 16 were removed without screening since 15 were only abstracts, and one was a duplicate. Then, 31 studies were excluded due to irrelevance. Nine were removed from the remaining 22 studies due to a non-compatible study design. The remaining 13 studies were included in the study [12-24] (Figure 1).

3.2. Characteristics of the included studies

All 13 studies enrolled were randomized clinical trials. Nine were Phase II, three were Phase III, and one was Phase I. The raw data of included studies are presented in (Table 1) (Table 2).

3.4. Main findings

The data of 1,062 patients were reviewed in this study, with 476 (44.8%) in the sunitinib alone group and 586 (55.2%) in the sunitinib plus erlotinib combination group. Males made up 632 (59.5%) of patients, with the remaining 430 (40.5%) being females. The mean age of all patients was 64 ± 5.03 years; in the sunitinib group, it was 64 ± 5.8 years; and in the sunitinib plus erlotinib group, it was 62.5 ± 2.4 years. Regarding ECOG assessment, a score of one in 649 (61.1%) cases was the most frequent, followed by a score of zero in 398 (37.5%), and a score of two in 12 (1.1%) patients. Out of the total study population, 759 (71.5%) were smokers, 174 (16.4%) were non-smokers, and in 129 (12.1%) cases, smoking status was not mentioned. Non-small cell lung cancer (NSCLC) was observed in 1013 (95.4%) patients, and small cell carcinoma was found in the remaining 49 (4.6%) patients. Regarding treatment duration, sunitinib was given for 7.1 ± 6.1 weeks on average, whereas sunitinib plus erlotinib was given for 9.4 ± 4.95 weeks. In total, 456 (42.9%) cases received one prior treatment, 393 (37%) reported no previous treatment, 94 (8.9%) had received two prior treatments, and 22 (2.1%) had taken more than two treatment therapies. In the remaining 97 (9.1%) patients, the history of prior therapy was not determined (Table 3). The most common adverse event was fatigue, reported in 299 patients (28.2%). Among them, 244 (81.6%) were in the sunitinib alone group, whereas 55 (18.4%) were in the combination group. Other frequent adverse events included diarrhea in 277 patients (26.0%), anorexia, and thrombocytopenia in 196 (18.5%) patients. Among the 277 patients with diarrhea, 151 (54.5%) were in the sunitinib alone group, while the remaining 126 (45.5%) were in the combination group. Similarly, out of the 196 patients with anorexia, 140 (71.4%) of them were among the patients receiving sunitinib alone, while 56 (28.6%) were in the combination group. The predominant hematological adverse events were thrombocytopenia and anemia in 196 (18.5%) and 191 (17.9%) patients, respectively. Dermatologically, 182 (17.1%) cases presented with skin rash and 36 patients (3.4%) had dry skin. The least common adverse event was fever or chills, which was present in 22 (2.1%) patients, 17 (77.3%) of them in the sunitinib alone group, and 5 (22.7%) of them in the group receiving both sunitinib and erlotinib (Table 4). Regarding the histology of NSCLC, the most prevalent was adenocarcinoma (50.6%), followed by squamous cell carcinoma (23.9%). In the sunitinib alone group, the median overall survival and progression-free survival (PFS) were 213 ± 70.9 days and 109.5 ± 76.6 days, respectively. However, the median overall survival and the PFS in the combination group were 270 ± 17.1 days and 96 ± 16.97 days, respectively. Out of the 586 (55.2%) patients who received both sunitinib and erlotinib, 165 (28.2%) of them still had progressive disease, and only 158 (26.96%) had stable disease. In the sunitinib alone group, only 99 (20.8%) patients had progressive disease, and 140 (29.4%) had stable disease (Table 3).

4. Discussion

Lung cancer, like many others, is a disease of the elderly, and the average age of patients at the time of diagnosis is usually around 70 [25]. The mean age of patients in this study was 64 years in both groups. In 2020, lung cancer was responsible for 11.4% of the total cases of cancer and 18% of deaths due to cancer [26]. The incidence of lung cancer tends to be higher in males as compared to females; however, many attribute this to the differences in smoking patterns between the two genders [27]. Accordingly, in this study, males (59.5%) were more common than females (40.5%). Many risk factors have been considered in the etiology of this disease, such as radon, asbestos, pollution, and air quality, all of which are environmental risk factors. Yet, the most important risk factor is smoking since the combustion of tobacco can produce up to 60 known carcinogens, with polyaromatic hydrocarbons being the most significant [6]. Out of the 1,062 patients included in this study, smoking status was known for 933 (87.9%) of them, with 759 (71.5%) identified as smokers and 174 (16.4%) as non-smokers. Lung cancer is classified into two main types: small cell carcinoma (15%) and NSCLC (85%) [7]. In the current study, 1,013 (95.4%) patients were found to have NSCLC, with the remaining 49 (4.6%) patients presenting with small cell carcinoma.

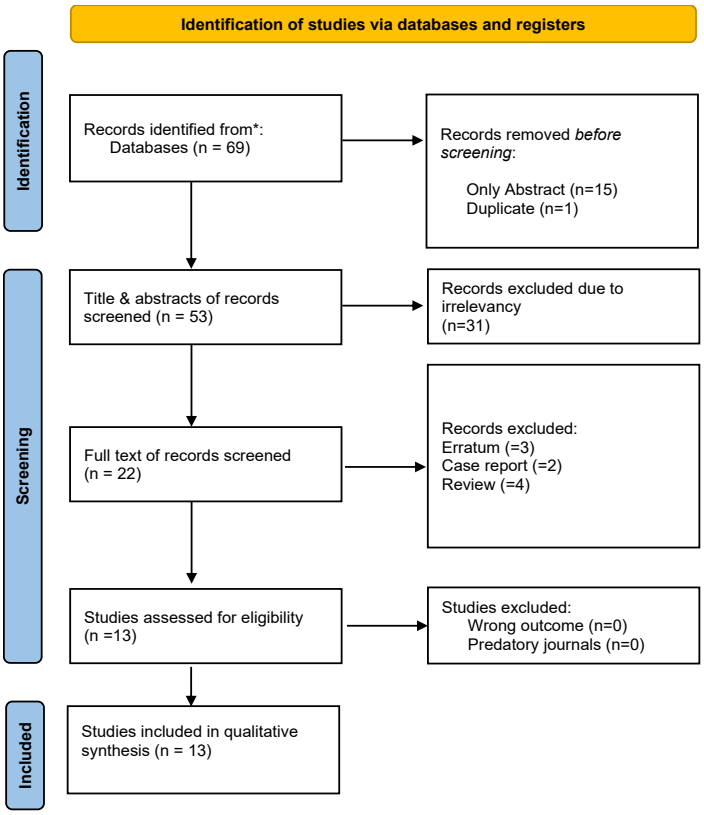

Figure 1. Study selection PRISMA flow chart

In addition, NSCLC is further divided into its subtypes. Adenocarcinoma, accounting for 40% of all cases of lung cancer, is considered the most common subtype of NSCLC, followed by squamous cell carcinoma (25-30%) and large cell carcinoma (5-10%) [28]. Similar patterns were observed in this study, as adenocarcinoma, with 513 (50.6%) cases, was deemed the most frequent. This was followed by squamous cell carcinoma (23.9%), large cell carcinoma (5.3%), and

Barw Medical Journal | 2024;2(3):57-64 | https://doi.org/10.58742/bmj.v2i2.95

Table 1: The raw data of each included study.

Author	Year of publication	Type of Therapy	Phase of clinical trial	No. of patients	Gender		Median Age	Smoking Status			ECOG Status				Type of lung cancer		Histology of NSCLC				
					Male	Female		Yes	No	N/A	0	1	2	N/A	Small cell Cancer	NSCLC	SCC	Adeno-carcinoma	Bronchoalveolar Carcinoma	Large cell Carcinoma	N/A
Socinski et al [12]	2013	Sunitinib	2	63	41	22	60	50	10	3	28	35	0	0	0	63	14	40	2	2	5
Baggstrom et al [13]	2017	Sunitinib	3	106	49	57	65	101	5	0	40	66	0	0	0	106	31	53	0	4	18
Reynolds et al [14]	2013	Sunitinib	2	63	32	31	78.4	0	0	63	17	46	0	0	0	63	0	0	0	0	63
Novello et al [15]	2009	Sunitinib	2	47	27	20	60	40	5	2	22	24	1	0	0	47	7	25	2	3	10
Han et al [16]	2013	Sunitinib	2	24	22	2	65	0	0	24	1	15	8	0	24	0	N/A	N/A	N/A	N/A	N/A
Scagliotti et al [17]	2012	Sunitinib and Erlotinib	3	480	297	183	61	384	96	0	184	294	0	0	0	480	135	261	12	17	55
Blumenschein et al [18]	2012	Sunitinib and Erlotinib	2	30	18	12	64	22	8	0	10	20	0	0	0	30	8	21	0	1	0
Novello et al [19]	2011	Sunitinib	2	64	39	25	61	29	35	0	35	28	1	0	0	64	12	40	1	2	9
Groen et al [20]	2013	Sunitinib and Erlotinib	2	65	39	26	59	57	7	1	21	43	0	1	0	65	15	36	0	6	8
Schneider et al [21]	2011	Sunitinib	2	16	8	8	66	0	0	16	5	10	1	0	16	0	N/A	N/A	N/A	N/A	N/A
Gervais et al [22]	2011	Sunitinib	2	84	53	31	60	76	8	0	29	54	1	0	0	84	20	28	3	19	14
Abdelraouf et al [23]	2015	Sunitinib	2	9	2	7	65	0	0	9	1	8	0	0	8	0	N/A	N/A	N/A	N/A	N/A
O'Mahar et al [24]	2011	Sunitinib and Erlotinib	1	11	5	6	64	0	0	11	5	6	0	0	0	11	0	9	0	0	2

N/A; non-available, NSCLC; non-small cell lung cancer, SCC, squamous cell carcinoma.

Table 2: Type, dose, duration and outcome of treatment in each study.

Author	No of patients	No. of previous treatment					Mean duration in days		Type of therapy	Dose of drug in (mg/day)		Outcome				Median Survival in Days	
		0	1	2	>2	N/A	Erlotinib	Sunitinib		Erlotinib	Sunitinib	Partial Response	Stable Disease	Progressive Disease	Not mentioned	Overall survival	Progression free survival
Socinski et al [12]	63	0	25	30	8	0	N/A	11	Sunitinib	N/A	50	7	18	3	35	164	84
Baggstrom et al [13]	106	23	83	0	0	0	N/A	N/A	Sunitinib	N/A	37.5	5	0	51	50	351	129
Reynolds et al [14]	63	27	36	0	0	0	N/A	6	Sunitinib	N/A	37.5	4	34	9	16	174	90
Novello et al [15]	47	0	19	18	10	0	N/A	4	Sunitinib	N/A	37.5	1	11	N/A	35	258	81
Han et al [16]	24	0	21	3	0	0	N/A	6.8	Sunitinib	N/A	50	2	7	14	1	180	42
Scagliotti et al [17]	480	340	136	4	0	0	18.9	18.6	Sunitinib and Erlotinib	150	37.5	46	155	156	123	270	108
Blumenschein et al [18]	30	0	20	8	2	0	9.4	4	Sunitinib and Erlotinib	150	37.5	3	N/A	3	24	N/A	N/A
Novello et al [19]	64	0	44	8	1	0	N/A	52	Sunitinib	N/A	37.5	1	18	9	36	176	282
Groen et al [20]	65	0	39	23	1	0	8.4	8.4	Sunitinib and Erlotinib	150	37.5	3	N/A	N/A	62	246	84
Schneider et al [21]	16	0	16	0	0	0	N/A	4	Sunitinib	N/A	50	11	2	0	3	246	186
Gervais et al [22]	84	0	0	0	0	84	N/A	11	Sunitinib	N/A	50	12	47	9	16	312	162
Abdelraouf et al [23]	9	2	7	0	0	0	N/A	7.4	Sunitinib	N/A	37.5	1	3	4	1	N/A	N/A
O'Mahar et al [24]	11	1	10	0	0	0	9.3	9.3	Sunitinib and Erlotinib	150	33	1	3	6	1	279	N/A

N/A; non-available

Barw Medical Journal | 2024;2(3):57-64 | https://doi.org/10.58742/bmj.v2i2.95

Table 3: The baseline characteristics of the patients.

Variables	Number of patients (1092)
Number of patients per treatment group	
Sunitinib	476 (44.8%)
Sunitinib + Erlotinib	586 (55.2%)
Median age (years) ± SD	
All patients	64 ± 5.03
Sunitinib	64 ± 5.8
Sunitinib + Erlotinib	62.5 ± 2.4
Sex	
Male	632 (59.5%)
Female	430 (40.5%)
Phase of clinical trial	
Phase 1	1 (7.7%)
Phase 2	9 (69.2%)
Phase 3	3 (23.1%)
ECOG Status	
Score 0	398 (37.5%)
Score 1	649 (61.1%)
Score 2	12 (1.1%)
Not mentioned	3 (0.3%)
Smoking Status	
Smoker	759 (71.5%)
Non-smoker	174 (16.4%)
Not mentioned	129 (12.1%)
Type of lung cancer	
Small cell carcinoma	49 (4.6%)
Non-Small cell carcinoma	1013 (95.4%)
Histology of non-small cell lung cancer	
Squamous cell carcinoma	242 (23.9%)
Adenocarcinoma	513 (50.6%)
Bronchoalveolar	20 (2.0%)
Large cell carcinoma	54 (5.3%)
Not mentioned	184 (18.2%)
Duration of drug administration (weeks) ± SD	
Sunitinib	7.1 ± 6.1
Sunitinib with Erlotinib	9.4 ± 4.95
Number of previous treatments	
No previous treatment	393 (37.0%)
1 previous treatment	456 (42.9%)
2 previous treatments	94 (8.9%)
More than 2 previous treatments	22 (2.1%)
Not mentioned	97 (9.1%)
Response to Sunitinib	
Partial response	44 (9.2%)
Stable disease	140 (29.4%)
Progressive disease	99 (20.8%)
Not mentioned	193 (40.6%)
Response to Sunitinib + Erlotinib	
Partial response	53 (9.0%)
Stable disease	158 (27%)
Progressive disease	165 (28.2%)
Not mentioned	210 (35.8%)
Median survival in Sunitinib (days) ± SD	
Overall survival	213 ± 70.9
Progression-free survival	109.5 ± 76.6
Median survival in Sunitinib + Erlotinib (days) ± SD	
Overall survival	270 ± 17.1
Progression free survival	96 ± 16.97

Table 4: The difference in adverse events between the different therapy groups.

Adverse events	Total	Sunitinib	Sunitinib + Erlotinib
Hematological			
Anemia	191 (100%)	117 (61.3%)	74 (38.7%)
Leuko-cytopenia	75 (100%)	72 (96%)	3 (4%)
Neutropenia	143 (100%)	103 (72%)	39 (28%)
Thromb-Ocytopenia	196 (100%)	147 (75%)	49 (25.0%)
Gastrointestinal			
Nausea	168 (100%)	124 (73.8%)	44 (26.2%)
Vomiting	129 (100%)	84 (65.1%)	45 (34.9%)
Diarrhea	277 (100%)	151 (54.5%)	126 (45.5%)
Constipation	62 (100%)	62 (100%)	0 (0%)
Anorexia	196 (100%)	140 (71.4%)	56 (28.6%)
Dermatological			
Skin rash	182 (100%)	68 (37.4%)	114 (62.6%)
Dry Skin	36 (100%)	7 (19.4%)	29 (80.6%)
Others			
Fever/Chills	22 (100%)	17 (77.3%)	5 (22.7%)
Fatigue	299 (100%)	244 (81.6%)	55 (18.4%)
Hypertension	78 (100%)	72 (90%)	6 (10%)
Cough	51 (100%)	43 (84.3%)	8 (15.7%)
Dyspnea	71 (100%)	63 (88.7%)	8 (11.3%)
Headache	34 (100%)	34 (100%)	0 (0%)
Pain	104 (100%)	96 (92.3%)	8 (7.7%)
Weight Loss	30 (100%)	30 (100%)	0 (0%)

can be secondary to metastasis. Furthermore, paraneoplastic symptoms such as kidney stones occurring due to hypercalcemia can also be present. Coughing, which is present in 50% to 75% of the patients, is considered the typical symptom, followed by dyspnea in 25-40%, chest pain in 20-40%, and hemoptysis in 15-30% of the cases [1]. One way to measure lung cancer patients' performance status is through the Eastern Cooperative Oncology Group (ECOG). The ECOG status is a scale ranging from zero, which represents a fully active individual with no restriction, to four, which represents patients who are completely disabled, and five for patients who have died [29]. According to a study by Lilenbaum et al., 34% to 48% of all patients had an ECOG score of two or higher [30]. In contrast, in the present study, an ECOG score of one was presented in 649 (61.1%) patients, followed by a score of zero in 398 (37.5%) and a score of two in 12 (1.1%) patients. The ECOG status was not determined in three patients.

to be found in stage I and 8% of the cases in stage II [1]. Imaging tools such as computerized tomography (CT) scans and magnetic resonance imaging (MRI) are usually the initial step in the diagnosis and staging of lung cancer [31,32]. Nowadays, patients who are considered high-risk, such as those with a history of heavy smoking, can undergo screening with low-dose CT (LDCT) scans to diagnose the disease in its early stages [33]. If the cancer is detected in its early stages, thoracic surgery to resect the mass is deemed the standard treatment when the patient is fit enough to undergo surgery [34]. Other forms of management include radical radiotherapy, radiofrequency, microwave ablation, and systemic therapies, a field that seems to be in continuous evolution. Due to the advancement of chemotherapeutic agents used in NSCLC, many agents have become more targeted and tailored to the specific needs of each patient [35]. The first targeted therapy produced for NSCLC was gefitinib, an oral agent that works by inhibiting a tyrosine kinase

receptor named epidermal growth factor receptor (EGFR), which is responsible for upregulating cellular proliferation and DNA synthesis [34]. Erlotinib is another tyrosine kinase-inhibitor targeted therapy used for EGFR-positive NSCLC patients [35]. This agent can be used alone or with other tyrosine kinase inhibitors, such as sunitinib. Sunitinib works by inhibiting vascular growth factor receptors 1, 2, and 3 (VEGFR-1, VEGFR-2, and VEGFR-3) as well as platelet-derived growth factor receptors [17].

By the time the disease is diagnosed, it has progressed to the late Sunitinib, when used alone in the treatment of NSCLC, may yield promising results. In a study conducted by Socinski et al., 11.1% of the patient population was reported to have a partial response to the treatment, with 28.6% having a stable disease. Moreover, the median PFS of the patients was 84 days, whereas the median overall survival was 164 days [12]. In a clinical trial conducted by Reynold et al. on patients with NSCLC receiving sunitinib, out of 60 patients, 4 (6.7%) had a partial response, 34 (56.7%) had stable disease, 9 (15%) had progressive disease, and the response of the remaining 13 (21.7%) patients was not evaluated [14]. In this study, the response among the patients receiving sunitinib alone was similar to the Socinski et al. study since 9.2% reported a partial response and 29.4% had stable disease. However, the median PFS in our study for the sunitinib group was 109.5 days, and the median overall survival was 213 days, which were higher than those in the Socinski et al. study. Scagliotti et al. combined sunitinib with erlotinib for NSCLC management and found that 9.6% of the patients had a partial response, 32.3% had a stable disease, and 32.5% had disease progression. Furthermore, they found out that the median overall survival was 270 days, and the PFS was 108 days [17]. Within the 586 patients that received a combination of sunitinib and erlotinib in this systematic review, a partial response was reported in 9.0% of the population and stable disease in 27%, whereas 28.2% of patients had progressive disease. Additionally, the median overall survival was 270 days, while the PFS was 96 days. Another aspect to consider when comparing the therapy groups is their safety profile and the nature of adverse events they may induce. In the sunitinib alone group, the most common adverse events reported were fatigue, pain, nausea, and vomiting. This is different from the adverse events reported when sunitinib was combined with erlotinib since the most frequent adverse event was diarrhea, followed by fatigue, anorexia, and cough [12,17]. In the study conducted by Reynold et al. where patients received sunitinib alone, similar patterns were observed in adverse events as fatigue with 29 (48.3%) and diarrhea with 23 (38.3%) were the most common adverse events [14]. In the present study, the most common adverse event was fatigue (28.2%), followed by diarrhea (26.1%), anorexia (18.5%), thrombocytopenia (18.5%), and anemia (17.9%). All the adverse events were more common in the sunitinib alone group, except for skin rash and dry skin. A limitation of this study was the inability to determine the superiority of either treatment group over the other due to the lack of statistical results stemming from the nature of the data reported in the included studies. Additionally, the variability in the phases of the included clinical trials may have induced bias in the findings.

5. Conclusion

Adverse events may be encountered more frequently in treatment with sunitinib alone compared to the combination of sunitinib and erlotinib. However, sunitinib alone may result in higher disease stability and lower disease progression compared to the combination regimen. Nevertheless, the combination of sunitinib and erlotinib may yield a longer median overall survival.

Declarations

Conflicts of interest: The author(s) have no conflicts of interest to disclose.

Ethical approval: Not applicable, as systematic reviews do not require ethical approval.

Patient consent (participation and publication)**:** Not applicable.

Funding: The present study received no financial support.

Acknowledgements: None to be declared.

Use of AI: AI was not used in the drafting of the manuscript, the production of graphical elements, or the collection and analysis of data.

Authors' contributions: BAA and FHK were major contributors to the conception of the study, as well as to the literature search for related studies. HOA, ASA, HMR, and MNH were involved in the literature review, manuscript writing, and data analysis and interpretation. YMM, SSO, and DAH Literature review, final approval of the manuscript, and processing of the tables. RMA, DAO, HKA, SHK, SHM, and MQM were involved in the literature review, the study's design, and the manuscript's critical revision. FHK and HOA Confirmation of the authenticity of all the raw data. All authors approved the final version of the manuscript.

Data availability statement: Note applicable.

References

1. Faraz Siddiqui, and Abdul H Siddiqui. “Lung Cancer.” Nih.gov, StatPearls Publishing, 2019, www.ncbi.nlm.nih.gov/books/NBK482357/
2. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. Contemporary Oncology/Współczesna Onkologia. 2021 ;25(1):45-52. doi:10.5114/wo.2021.103829
3. de Groot P, Munden RF. Lung cancer epidemiology, risk factors, and prevention. Radiologic Clinics. 2012 ;50(5):863-76. doi:10.1016/j.rcl.2012.06.006
4. Brown JS, Eraut D, Trask C, Davison AG. Age and the treatment of lung cancer. Thorax. 1996 ;51(6):564-8. doi:10.1136/thx.51.6.564
5. Mingomataj E, Krasniqi M, Dedushi K, Sergeevich KA, Kust D, Qadir AA, et al. Cancer Publications in One Year (2023): A Cross-Sectional Study. Barw Medical Journal. 2024. doi:10.58742/g9q9t715

6. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Translational lung cancer research. 2018 ;7(3):220. doi:10.21037/tlcr.2018.05.06
7. Sher T, Dy GK, Adjei AA. Small cell lung cancer. InMayo Clinic Proceedings 2008 Mar 1 (Vol. 83, pp. 355-367). Elsevier. doi:10.4065/83.3.355
8. Chirieac LR, Dacic S. Targeted therapies in lung cancer. Surgical pathology clinics. 2010 ;3(1):71-82. doi:10.1016/j.path.2010.04.001
9. Ali RM, Kakamad FH, Abdullah HO, Abdulla SH, Ahmed SF, Amin BJ, et al. Pembrolizumab (Anti-PD-1) Immunotherapy in Malignant Pleural Mesothelioma: A Systematic Review of the Current Literature. Barw Medical Journal. 2023. doi:10.58742/bmj.v1i2.34
10. Omar SS, Ali RH, Abdullah SH, Hussein DM, Radha BM, Latif AB, et al. Role of Durvalumab (Anti-PD-L1) in the Management of Mesothelioma: A Systematic Review of the Current Literature. Barw Medical Journal. 2023 Dec 5. *doi:N/A*
11. Muhialdeen AS, Ahmed JO, Baba HO, Abdullah IY, Hassan HA, Najar KA, et al. Kscien's list; a new strategy to discourage predatory journals and publishers (second version). Barw Medical Journal. 2023. doi:10.58742/bmj.v1i1.14
12. Socinski MA, Novello S, Brahmer JR, Rosell R, Sanchez JM, Belani CP, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non–small-cell lung cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008 ;26(4):650. doi:10.1200/JCO.2007.13.9303
13. Baggstrom MQ, Socinski MA, Wang XF, Gu L, Stinchcombe TE, Edelman MJ, et al. Maintenance sunitinib following initial platinum-based combination chemotherapy in advanced-stage IIIB/IV non–small cell lung cancer: a randomized, double-blind, placebo-controlled phase III study—CALGB 30607 (Alliance). Journal of Thoracic Oncology. 2017;12(5):843-9. doi:10.1016/j.jtho.2017.01.022
14. Reynolds C, Spira AI, Gluck L, Mueller SE, Zhan F, Boehm KA, et al. Sunitinib malate in previously untreated, nonsquamous, non-small cell lung cancer patients over the age of 70 years: results of a Phase II trial. Investigational new drugs. 2013 ;31:1330-8. doi:10.1007/s10637-013-9985-0
15. Novello S, Scagliotti GV, Rosell R, Socinski MA, Brahmer J, Atkins J, et al. Phase II study of continuous daily sunitinib dosing in patients with previously treated advanced non-small cell lung cancer. British journal of cancer. 2009 ;101(9):1543-8. doi:10.1038/sj.bjc.6605346
16. Han JY, Kim HY, Lim KY, Han JH, Lee YJ, Kwak MH, et al. A phase II study of sunitinib in patients with relapsed or refractory small cell lung cancer. Lung Cancer. 2013 ;79(2):137-42. doi:10.1016/j.lungcan.2012.09.019
17. Scagliotti GV, Krzakowski M, Szczesna A, Strausz J, Makhson A, Reck M, et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non–small-cell lung cancer: a phase III trial. Journal of clinical oncology. 2012 ;30(17):2070-8. doi:10.1200/JCO.2011.39.2993
18. Blumenschein Jr GR, Ciuleanu T, Robert F, Groen HJ, Usari T, Ruiz-Garcia Aet al. Sunitinib Plus Erlotinib for the Treatment of Advanced/Metastatic Non–Small-Cell Lung Cancer: A Lead-In Study. Journal of Thoracic Oncology. 2012;7(9):1406-16. doi:10.1097/JTO.0b013e31825cca1c
19. Novello S, Camps C, Grossi F, Mazieres J, Abrey L, Vernejoux JM, et al. Phase II study of sunitinib in patients with non-small cell lung cancer and irradiated brain metastases. Journal of Thoracic Oncology. 2011 ;6(7):1260-6. doi:10.1097/JTO.0b013e318219a973
20. Groen HJ, Socinski MA, Grossi F, Juhasz E, Gridelli C, Baas P, et al. A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic non-small-cell lung cancer (NSCLC). Annals of oncology. 2013 ;24(9):2382-9. doi:10.1093/annonc/mdt212
21. Schneider BJ, Gadgeel SM, Ramnath N, Wozniak AJ, Dy GK, Daignault S, et al. Phase II trial of sunitinib maintenance therapy after platinum-based chemotherapy in patients with extensive-stage small cell lung cancer. Journal of Thoracic Oncology. 2011 ;6(6):1117-20. doi:10.1097/JTO.0b013e31821529c3
22. Gervais R, Hainsworth JD, Blais N, Besse B, Laskin J, Hamm JT, et al. Phase II study of sunitinib as maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer. Lung Cancer. 2011 ;74(3):474-80. doi:10.1016/j.lungcan.2011.05.004
23. Abdelraouf F, Smit E, Hasan B, Menis J, Popat S, van Meerbeeck JP, et al. Sunitinib (SU11248) in patients with chemo naive extensive small cell lung cancer or who have a 'chemosensitive'relapse: a single-arm phase II study (EORTC-08061). European Journal of Cancer. 2016 ;54:35-9. doi:10.1016/j.ejca.2015.10.016
24. O'Mahar SE, Campbell TC, Hoang T, Seo S, Kim K, Larson MM,et al. Phase I study of sunitinib and erlotinib in advanced nonsquamous non-small cell lung cancer. Journal of Thoracic Oncology. 2011 ;6(5):951-3. doi:10.1097/JTO.0b013e31820db227
25. Blumenschein Jr GR, Ciuleanu T, Robert F, Groen HJ, Usari T, Ruiz-Garcia, et al. Sunitinib Plus Erlotinib for the Treatment of Advanced/Metastatic Non–Small-Cell Lung Cancer: A Lead-In Study. Journal of Thoracic Oncology. 2012 ;7(9):1406-16. doi:10.1097/JTO.0b013e31825cca1c
26. Lung Cancer Statistics | How Common is Lung Cancer? [Internet]. www.cancer.org. Available from: https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html#:~:text=Most%20people%20diagnosed%20with%20lung
27. Li C, Lei S, Ding L, Xu Y, Wu X, Wang H, et al. Global burden and trends of lung cancer incidence and mortality. Chinese Medical Journal. 2023 ;136(13):1583-90. doi:10.1097/CM9.0000000000002529
28. Gee K, Yendamuri S. Lung cancer in females—sex-based differences from males in epidemiology, biology, and outcomes: a narrative review. Translational Lung Cancer Research. 2024 ;13(1):163. doi:10.21037/tlcr-23-744
29. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JH, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. Journal of thoracic oncology. 2015;10(9):1243-60. doi:10.1097/JTO.0000000000000630
30. ECOG-ACRIN Cancer Research Group. ECOG Performance Status Scale [Internet]. ECOG-ACRIN Cancer Research Group. 2022. Available from: https://ecog-acrin.org/resources/ecog-performance-status/
31. Lilenbaum RC, Cashy J, Hensing TA, Young S, Cella D. Prevalence of poor performance status in lung cancer patients: implications for research. Journal of Thoracic Oncology. 2008 ;3(2):125-9. doi:10.1097/JTO.0b013e3181622c17
32. Lung Cancer Diagnosis [Internet]. www.hopkinsmedicine.org. 2021. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/lung-cancer/lung-cancer diagnosis#:~:text=Diagnostic%20Procedures
33. Nooreldeen R, Bach H. Current and future development in lung cancer diagnosis. International journal of molecular sciences. 2021 ;22(16):8661. doi:10.3390/ijms22168661
34. Jones GS, Baldwin DR. Recent advances in the management of lung cancer. Clinical Medicine. 2018;18(Suppl 2):s41. doi:10.7861/clinmedicine.18-2s-s41
35. Carter J, Tadi P. Erlotinib [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Apr 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554484/#:~:text=Erlotinib%20is%20a%20medication%20used%20in%20the%20management%20and%20treatment