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Evaluation of Addition of Nintedanib to Corticosteroids for Treatment of Radiation Pneumonitis in Patients Undergoing Treatment for Lung Cancers in India

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Abstract:

Introduction: Radiation pneumonitis (RP) is a significant complication of chest cancer radiotherapy, often leading to severe respiratory distress and reduced survival rates. Current treatment guidelines primarily recommend corticosteroids, although their efficacy in preventing RP-induced pulmonary fibrosis is inconclusive. Nintedanib, a tyrosine kinase inhibitor, has shown promise in treating pulmonary fibrosis by targeting key inflammatory mediators. However, its application in RP management remains unexplored, particularly in the Indian population.

Methods: A prospective, randomized, open-label study was conducted on lung cancer patients with RP, involving two groups: one receiving nintedanib in combination with prednisone, and the other receiving prednisone monotherapy. The primary endpoint was the proportion of patients free from acute pulmonary exacerbations within one year. Secondary endpoints included the total number of exacerbations and quality of life measures.

Results: Among 39 enrolled patients, 34 completed the study. Significantly more patients in the nintedanib group (80%) remained free from exacerbations compared to the prednisone group (50%). The mean number of exacerbations was significantly lower in the nintedanib group (0.77) compared to the prednisone group (1.28). Adverse events were minimal, with diarrhoea and nausea reported as the most common side effects in the nintedanib group.

Discussion: This study demonstrates a statistically significant reduction in acute pulmonary exacerbations within one year by adding nintedanib to prednisone for RP treatment. Nintedanib's potential in targeting shared fibrosis mechanisms across various interstitial lung diseases, as evidenced in previous trials, suggests its efficacy in RP management. While diarrhea and nausea were common side effects, nintedanib was generally well-tolerated.

Conclusion: This study provides crucial insights into the effectiveness of nintedanib as an adjunct to corticosteroids in managing RP. The significant reduction in exacerbations and favorable safety profile suggest a potential paradigm shift in RP treatment. Further, larger-scale confirmatory studies are warranted to validate these findings and potentially integrate nintedanib into routine clinical practice for RP in lung cancer patients.

Keywords: Radiation Pneumonitis, Nintedanib, Corticosteroids, Pulmonary Fibrosis, Lung Cancer, India

Introduction

Radiation pneumonitis (RP) is one of the common adverse effects observed when radiotherapy is used for chest cancers [1,2]. RP can present clinically as one or more of the following symptoms: non-productive cough, dyspnoea on exertion, low grade fever, hypoxemia; severe cases may progress to respiratory failure. All these symptoms appear within the range of 4 to 32 weeks from the end of radiotherapy [3,4]. Course of RP is quite unpredictable, majority of patients frequent acute exacerbations of pulmonary symptoms and gradually progress to fibrosis of lung [5–7]. Severe RP has less chances of survival, to the extent that 50% of individuals with severe RP, succumb to death [8,9]. Risk of development of RP is associated with radiation dose, amount of pulmonary parenchyma exposed to radiation and also to amount of cardiac tissue exposed to radiation [4,10,11].

Various inflammatory mediators are involved in pathogenesis of RP – Transforming Growth Factor β, Vascular Endothelial Growth Factor, Tissue Necrosis Factor, Platelet Derived Growth Factor, Interleukin-6, Interleukin-8 and Nuclear Factor-κβ along with other cytokines [4,12]. These growth factors and cytokines are released after radiation, resulting in inflammation which manifests as sub-acute RP. In long run, fibroblasts and myofibroblasts get activated by these cytokines, resulting in fibrin deposition causing irreversible anatomical and physiological damage to lung tissue – pulmonary fibrosis [13].

Current treatment guidelines for RP prescribe corticosteroids for more than two months [4,12]; which is often encountered with prominent adverse effects in short term as well as long term [14]. Despite corticosteroids being routinely used for prevention and treatment of pulmonary fibrosis, there is no evidence that corticosteroids can prevent pulmonary fibrosis due to radiation pneumonitis [15,16]. Apart from corticosteroids, ACE inhibitors, amifostine, and pentoxifylline are also tried when there is no response to corticosteroids but these agents have not proved their efficacy comparable to corticosteorids [3,17]. A lacuna exists in proper treatment of radiation pneumonitis for which evidence based management is essential.

Nintedanib is a tyrosine kinase inhibitor, approved for use in pulmonary fibrosis. Nintedanib acts by antagonizing important inflammatory mediators such as fibroblast growth factor receptor 1 and 3 (FGFR 1 and 3), platelet derived growth factor receptor α and β (PDGFR α and β) and vascular endothelial growth factor receptor 1, 2 and 3 (VEGFR 1, 2, and 3). Various studies have explored to utilize these growth factors as therapeutic targets to treat or prevent pulmonary fibrosis [18–20]. Antifibrotic and antiinflamamtory action of Nintedanib has been proved in animal models, where lung fibrosis was induced using bleomycin or silica [21,22]. Clinical trials in idiopathic pulmonary fibrosis patients have demonstrated retarded progression of disease by Nintedanib, this was appreciated clinically by observing the retarded rate of decline of forced vital capacity [23–25]. Other clinical studies have also demonstrated the ability of Nintedanib to decrease risk of acute exacerbations of idiopathic pulmonary fibrosis [26,27]. Results of INBUILD and SENCIS trials have proved retarded decline of FVC in chronic fibrosing interstitial lung disease (ILD) and systemic sclerosis associated with ILD due to Nintedanib [28].

Pathophysiology of RP is similar to IPF and Nintedanib is being used for the latter. Current evidence for treatment of radiation pneumonitis outside corticosteroids is limited especially regarding Nintedanib. We could not find substantial studies where Nintedanib has been tried for RP in Indian patients of lung cancer. Hence, we decided to take up this study.

Materials and Methods

This was a prospective, randomized, open label study done on patients undergoing treatment for lung cancer at Department of Radiation Oncology, Viswabharathi Cancer Hospital, Kurnool, Andhra Pradesh; from February 2022 to August 2023. MAS was a part time consultant pulmonologist at Viswabharathi Cancer Hospital who followed up with study participants and collected data. Prior approval of study protocol was obtained from institutional ethics committee of Viswabharathi Medical College and General Hospital.

MGM was requested to visit Viswabharathi cancer hospital for patient selection and treatment. SV was a full time consultant at this institute, he assisted MAS in following-up with patients and data collection.

Patients who were 18 years of age or older and had recently been diagnosed with Radiation Pneumonitis (RP) of grade G2 to G4, as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and had a history of lung cancer treated with the intention of providing a definitive cure, were enrolled in the study. To be eligible, patients needed to have received radiation therapy for lung cancer between 4 weeks and 9 months prior to enrolment and have a Karnofsky Performance Status (KPS) score of 70 or higher.

Exclusion criteria encompassed current oral steroid use for a duration of 4 weeks or more prior to registration, ongoing radiation therapy, systemic therapy, or hormonal therapy, as well as a history of bleeding disorder, thrombotic events, or liver disorder. Patient recruitment was carried out by the investigators and their respective research teams. Each and every patient was explained in their understandable language regarding purpose and procedure of study in front of their relatives. Written consent was taken from every patient.

Participation of patients for this study was on their free will and they were informed about the option to drop out of study at any time.

Patients who met the eligibility criteria were categorized based on the severity of RP (Grade 2 as opposed to 3 or 4) and whether they had previously started taking steroids or were steroid-naïve. A randomizer application was employed to assign unique identification numbers to all participants for the purpose of randomization. Subsequently, the patients were allocated randomly, with a 1:1 ratio, to either the group receiving Nintedanib in conjunction with prednisone (group 1) or the group receiving prednisone monotherapy (group 2).

For group 1 patients, Nintedanib was administered orally at an initial dosage of 150 mg twice daily for a span of 12 weeks. Simultaneously, prednisone was initiated at a daily oral dose of 40 mg for a fortnight, followed by a tapering regimen of 10 mg every two weeks for a period of four weeks, succeeded by 10 mg for one week, and then 5 mg for another week, culminating in a total prednisone duration of eight weeks (Fig 1a).

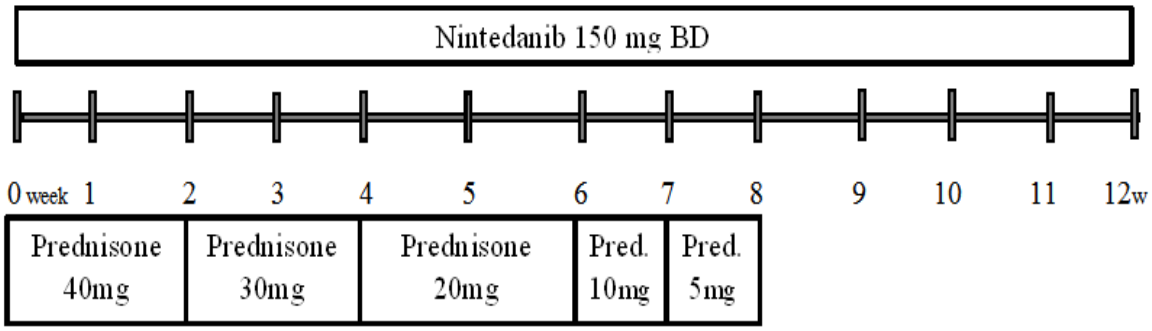

Figure 1a: Treatment pattern

For group 2 patients, Nintedanib was not given, and oral prednisone was given in same manner as group 1. Any adjustments in the prednisone taper or increments in dosage were allowed if deemed clinically necessary.

Hospital visits for safety and tolerability assessments of the investigational drug, as well as evaluations for acute pulmonary exacerbations, were conducted at three-week intervals during the initial three months, followed by assessments at five, six, nine, and thirteen-month marks (Fig 1)

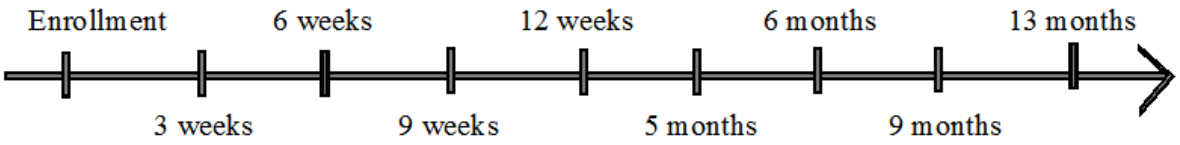

Figure 1: Time line of Follow up of patients

Patient-reported outcomes were gathered using the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) surveys and the St. George's Respiratory Questionnaire (SGRQ).

The primary outcome was the proportion of patients who were free from acute pulmonary exacerbations within one year of enrolment. Acute pulmonary exacerbations were defined as unexplained worsening or development of new cough, dyspnoea, hypoxia, or pneumonia lasting more than 4 days with new or worse diffuse pulmonary infiltrates on CT chest without significant pneumothorax or pleural effusion, and exclusion of alternative causes such as pneumonia, congestive heart failure, pulmonary emboli, or cancer progression. Exacerbations in the first 2 weeks of study treatment were not counted towards the primary endpoint to allow for adequate resolution of the initial presenting symptoms. Secondary endpoints include the total number of exacerbations. Exploratory endpoints included quality of life measures by SGRQ and PRO-CTCAE. Adverse events were monitored for any G4 or higher toxicities, and the sequential probability ratio test was used to define a stopping rule.

The primary objective was to determine the percentage of patients who experienced no acute pulmonary exacerbations within a year of their enrolment. These exacerbations were characterized by an unexplained deterioration or the onset of new symptoms like coughing, shortness of breath, hypoxia, or pneumonia lasting over four days; along with evidence of new or worsened diffuse pulmonary infiltrates on CT chest scan, with no significant pneumothorax or pleural effusion, and after ruling out other potential causes such as pneumonia, congestive heart failure, pulmonary emboli, or cancer progression. Exacerbations occurring in the initial two weeks of the treatment phase were not included in the primary assessment to allow for proper resolution of the initial symptoms. Any adverse events reported by patients or observed clinically were recorded as safety parameters.

Statistical Analysis

All recorded data from study was entered in Microsoft excel sheet as numbers and percentages. Median and range of all baseline parameters were calculated using excel. Differences between groups was illustrated with bar diagrams which were drawn

using excel. Comparison of two groups was done using unpaired t test, which was run in excel. P value < 0.05 was considered as statistically significant.

Results

During this 18-month study, a total of 39 individuals were enrolled. Following randomization, 5 participants dropped out of the study. Consequently, 34 subjects were included in the ultimate analysis, with 20 in the nintedanib group and 14 in the prednisone group (Fig 2).

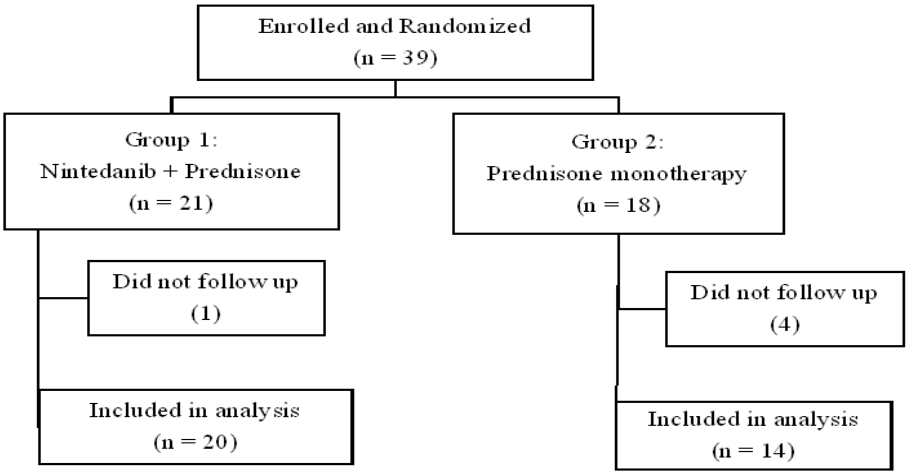

Figure 2: Randomization of patients

The initial attributes of trial participants are detailed in Table 1.

Table 1: Baseline characteristics of study population

Characteristic	Overall (n=34) [{median (range)} /{n(%)}]	Nintedanib+Prednisone (n=20) [{median (range)} /{n(%)}]	Prednisone (n=14) [{median (range)} /{n(%)}]	p value
Age (years) [median (range)]	62 (41-74)	61 (41-70)	60 (43-74)	p > 0.05
Gender				
Male	11 (32.35%)	7 (35%)	5 (35.71%)	p > 0.05
Female	23 (67.65%)	13 (65.00%)	9 (64.29%)	p > 0.05
Smoking Status				
Former	27 (79.41%)	16 (80.00%)	11 (78.57%)	p > 0.05
Never	7 (20.59%)	4 (20.00%)	3 (21.43%)	p > 0.05
KPS [median (range)]	90 (70-100)	90 (70-100)	90 (70-100)	p > 0.05
Radiation Dose				
48-50 Gy / 4-5 fx	9 (26.7%)	5 (25.00%)	4 (28.57%)	p > 0.05
45-60 Gy / 10-20 fx	3 (8.82%)	2 (10.00%)	1 (07.14%)	p > 0.05
45-66 Gy / 25-35 fx	22 (64.70%)	13 (65.00%)	9 (64.29%)	p > 0.05
Pneumonitis Grade				
Grade 2	28 (82.35%)	16 (80.00%)	12 (85.71%)	p > 0.05
Grade 3	6 (17.65%)	4 (20.00%)	2 (14.29%)	p > 0.05

Prior Steroids	27 (79.41%)	14 (70.00%)	13 (92.86%)	p > 0.05
Cancer type				
NSCLC	28 (82.35%)	17 (85.00%)	11 (78.57%)	p > 0.05
SCLC	6 (17.65%)	3 (15.00%)	3 (21.42%)	p > 0.05
*KPS = Karnofsky Performance Status				

In terms of the radiation therapy course preceding trial admittance, 64.70% of patients received doses ranging from 45 to 66 Gy administered over 25 to 35 sessions (Table 1). 6 individuals in the nintedanib group and 5 in the placebo group presented with G3 pneumonitis at enrolment (Table 1). No participants exhibited G4 pneumonitis at baseline. A majority of the subjects (79.41%) initiated corticosteroid therapy within 4 weeks prior to enrolment. The median duration of prior steroid treatment for those who commenced before enrolment stood at 7 days [range 2 to 20 days] in the nintedanib group and 7 days [range 2 to 30 days] in the prednisone group. All the baseline characteristics were similar in both groups with no statistically significant difference (p>0.05).

16 (80%) patients in Nintedanib group and 7 (50%) patients in prednisone group did not report of any acute pulmonary exacerbation during the study period and this difference was statistically significant (p<0.05) (Table 2; Fig 3).

Table 2: Patients free from acute exacerbations

GROUP	n	%	p
nintedanib+prednisone (n=20)	16	80.00%	p<0.05
prednisone (n=14)	7	50.00%	

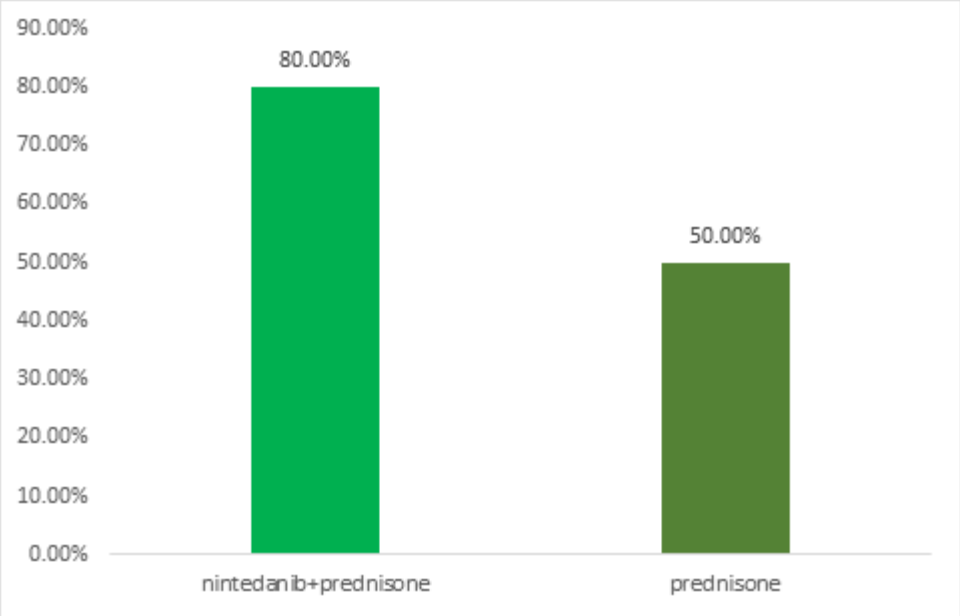

Figure 3: Patients free from acute exacerbations

Remarkably, even though there were more number of G3 pneumonitis in the nintedanib group, more participants from this group never complained of any exacerbation. Mean number of exacerbations in nintedanib group were 0.77 while that in prednisone group were 1.28 (p<0.05) (Table 3; Fig 4).

Table 3: mean acute exacerbations

GROUP	n	p
nintedanib+prednisone (n=20)	0.77	p<0.05
prednisone (n=14)	1.28	

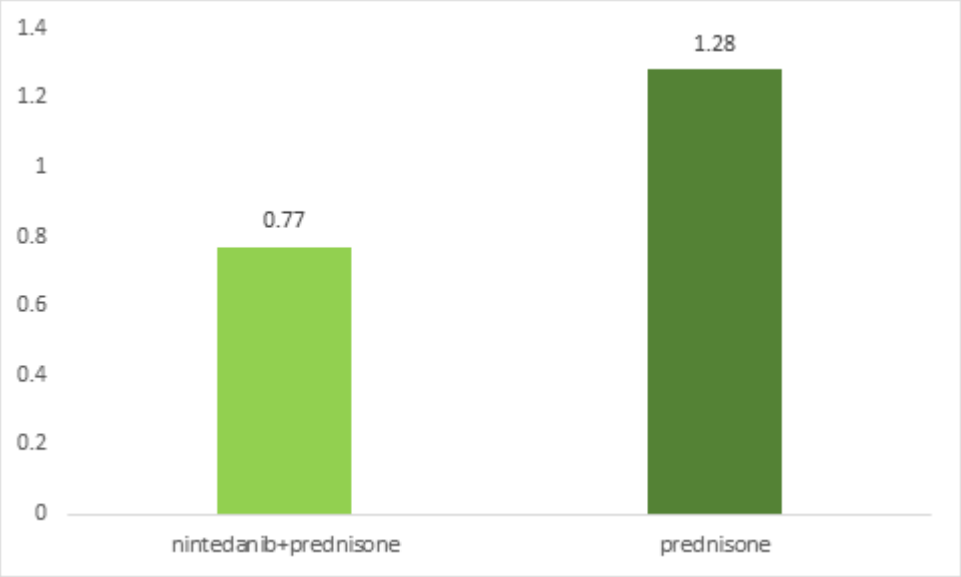

Figure 4: Mean no. of acute exacerbations

No serious untoward reactions were reported during the study from any group. 2 (10%) patients reported Diarrhoea and 2 (10%) nausea from Nintedanib group, while 1 (7.14%) reported diarrhoea and 1 (7.14%) nausea from prednisone group. Decreased platelet count and thromboembolic episode were observed in 1 (5%) patient each in Nintedanib group but such events were not seen in prednisone group. However total adverse events were lesser in Nintedanib group [10 (50%)] compared to prednisone group [10 (71.43%)] (Table 4).

Table 4: Adverse reactions

adverse event	nintedanib (n=20)	prednisone (n=14)
systemic		
fatigue	1 (5%)	1 (7.14%)
respiratory		
cough	-	2 (14.29%)
dyspnoea	1 (5%)	1 (7.14%)
hypoxia	1 (5%)	1 (7.14%)
gastrointestinal		
diarrhoa	2 (10%)	1 (7.14%)
nausea	2 (10%)	1 (7.14%)
cardiovascular		
hypertension	1 (5%)	1 (7.14%)
hematologic		
decreased platelet count	1 (5%)	-
decreased lymphocyte count	-	1 (7.14%)
thromboembolism	1 (5%)	-
skin		
rash		1 (7.14%)
total events reported	10 (50%)	10 (71.43%)

Discussion

This research demonstrated a statistically significant difference in reducing exacerbations within one year of adding nintedanib to prednisone. The efficacy of nintedanib in ameliorating outcomes in interstitial lung disease with progressive fibrosis, as observed in the INBUILD and SENICI trials, suggests that this drug can effectively target shared fibrosis mechanisms arising from different causes [23,28]. Although the primary focus of those studies was the rate of FVC decline, supplementary analysis of the INPULSIS trials in IPF revealed a significant reduction in the risk of a first acute exacerbation, reported as a serious adverse event, with Nintedanib [29,30]. Recent investigations have also commenced probing into the application of nintedanib in

radiation pneumonitis (RP) and radiation-induced fibrosis [31]. Preclinical experiments in mice have indicated that nintedanib mitigates late radiation-induced fibrosis [32]. Notably, in a recently published randomized trial of nintedanib as prophylaxis against RP, the placebo group experienced a higher number of clinically significant RP incidents compared to the nintedanib group [33].

In this study, the nintedanib group exhibited diarrhoea and nausea as the most prevalent adverse events. This aligns with other trial data, indicating that diarrhoea was a frequent side effect of nintedanib, with 65.9% of patients experiencing this in a meta-analysis of randomized trials [34]. Although nintedanib was generally well-tolerated in trials for idiopathic pulmonary fibrosis, additional safety monitoring is advisable if it is being considered for use in RP. Due to its angiogenesis inhibiting properties, nintedanib may increase the risk of bleeding [35]. However, a pooled analysis of clinical trials involving IPF patients showed no elevated bleeding rates with nintedanib compared to placebo [36]. In another study, one patient with squamous cell lung cancer treated with nintedanib experienced a Grade 5 haemorrhagic event [33] . In our study, three patients treated with nintedanib had squamous cell histology, and no bleeding adverse events were observed. Overall adverse effects were more in prednisone monotherapy group, this could be due to longer duration of steroid treatment, which was shortened in nintedanib group

The major limitation of this study is the limited number of patients. Furthermore, a small number of patients in both groups did not follow-up. Nevertheless, even with the modest enrolment and dropouts, there was a significant enhancement in freedom from exacerbations observed in the nintedanib arm at the designated 1-year analysis, in line with the study protocol. Augmented enrolment would have bolstered the robustness of these findings; hence, we advocate for a larger confirmatory study before considering the incorporation of nintedanib into routine clinical practice for Radiation Pneumonitis.

Given that the approved applications of nintedanib were expanded following its demonstrated efficacy in treating chronic fibrosing ILDs with varying causes, it becomes pertinent to investigate whether this drug could similarly enhance the progression from RP to pulmonary fibrosis. The enhancement in freedom from pulmonary exacerbations implies that the positive effect of nintedanib might arise from its capacity to ameliorate acute and subacute inflammation, modulated by the signalling pathways it inhibits [37]. This discovery aligns with the prolonged time to first acute exacerbation observed with nintedanib in the INPULSIS-2 trial for IPF [29]. Consequently, a potential area for future research would be to investigate whether nintedanib mitigates the severity of pulmonary exacerbations following radiation treatment, mirroring its potential impact in IP.

The growing utilization of immunotherapy in patients undergoing thoracic radiation therapy is likely a factor in the occurrence of RP [38]. The incorporation of adjuvant durvalumab for non-small cell lung cancer patients, following the demonstrated overall survival benefit in the PACIFIC trial, may elevate the risk of RP in comparison to chemoradiotherapy alone [39]. This underscores the significance of investigating RP treatment, as the onset of this complication can potentially hinder or interrupt the administration of adjuvant immunotherapy. Another contributing factor to the rise in RP cases in contemporary practice could be the adoption of high-dose radiation therapy and multiple treatment courses for managing oligometastatic disease[. The optimal timing, sequence, and duration of nintedanib and steroids for RP treatment have not been conclusively determined. Since nintedanib focuses on the pathways related to the shift from acute inflammation to chronic pulmonary fibrosis, we anticipate that the timing of nintedanib in relation to the initiation of steroids may not be crucial. This is because steroids are likely effective in managing the acute inflammatory phase.

Conclusion

This was the first prospective, randomized clinical study done in India for the treatment of Radiation Pneumonitis due to radiotherapy given for lung cancer. Though corticosteroids are standard treatment for treating RP, this study showed that acute exacerbations were more common despite corticosteroid monotherapy. Nintedanib addition to corticosteroid was efficacious than steroid monotherapy in suppressing acute exacerbations for 1 year. Addition of nintedanib has also reduced duration of corticosteroid therapy thus avoiding adverse effects of long term steroid therapy.

Authors Contributions

MGM, FZA and AP collectively conceptualized the idea for this research. Study design was prepared by FZA and SV which was reviewed by MGM and MAS. Patient selection and drug administration was done by MGM. Data collection and follow up was done by MAS and SV. Data analysis, statistical analysis and manuscript preparation was done by FZA and AP. Manuscript was reviewed by MAS and MGM.

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