Mini review

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Prognostic factors of the overall survival and disease progression in advanced non-small cell lung cancer patients in India: Mini review

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Abstract

Lung cancer is the most prevalent cancer among females and males, carrying the highest cancer-related mortality rates worldwide. Nearly two-thirds of patients present in the advanced stage at diagnosis requiring palliative therapy with chemotherapy and often radiotherapy, giving a variable response, too. Knowledge of prognostic factors might guide in tailoring the therapy in resource-limited countries. Hence, we reviewed the prognostic factors affecting overall survival and disease progression in advanced non-small-cell lung cancer patients.

Keywords: Lung cancer; chemotherapy; radiotherapy, prognostic factor; NSCLC.

Introduction

It has the highest cancer-related mortality rates worldwide [1].In India, lung cancer constitutes 6.9 percent of all new cancer cases and 9.3 percent of all cancer-related deaths in both sexes. It is the commonest cancer and cause of cancer-related mortality in men, with the highest reported incidences from Mizoram in males and females [2].

Non-small cell lung cancer (NSCLC) accounts for more than 80% of primary lung cancers, and out of these, approximately two-thirds of patients present in the advanced stage (Stage III and IV of 7th TNM staging) at diagnosis [3]. Chemotherapy with or without radiotherapy is the only treatment modality available at this stage which that too gives a variable response in terms of tumor size reduction and survival. However, with the advent of new chemotherapeutic regimens and targeted therapies, these patients' response rates and survival have improved significantly in recent years.

Palliative treatment in patients with advanced lung cancer yields a significant response in few patients. However, few show a progression of disease while others show equivocal reactions. Hence, knowledge of independent prognostic factors (patient, tumor, and treatment-based) that may predict response to chemotherapy/radiotherapy can be of immense help in improving our approach to the management of these patients. For example, knowledge of prognostic factors might guide the tailoring of the therapy, better monitoring of patients with poor prognostic factors. In addition, it can serve as a basis for future research to evaluate the causes of poor response.

Data from few international studies have tried to find prognostic factors that may predict a better outcome to chemotherapy in these patients. Clinical features like cough, grade of dyspnea, fever, significant weight loss are the simplest parameters that have been found to predict outcome in lung cancer patients after chemotherapy [4]. Patient characteristics like age, gender, performance status, smoking status, previous tuberculosis, co-morbidities are other factors that have been evaluated as predictors of response to chemotherapy in lung cancer [5, 6, 7]. Tumor-specific factors like baseline tumor size (based on RECIST score), no metastatic sites, tumor histology, baseline clinical-stage, malignant pleural effusion, and primary tumor localization have also been studied for their potential role in predicting tumor response [3, 5, 8, 9]. On the other hand, some biological factors [lactate dehydrogenase (LDH), uric acid, hypercalcemia, epidermal growth factor receptor (EGFR), alkaline phosphatase, leukocytosis, and neutrophil count] have also been evaluated as prognostic factors in advanced lung cancer [6, 10, 11, 12].

Altogether, there is a lack of uniformity in the factors that have been evaluated in these studies and a lack of consistency in the results. Moreover, there is a scarcity of data on the prog-

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nostic markers of response to chemotherapy from our geographical area. However, it is known that lung cancer behavior differs between different geographical areas and ethnicities."

Results

Table showing various studies with prognostic significant factors for advanced (inoperable stage III and stage IV) NSCLC patients treated with chemotherapy with or without radiotherapy.

Authors	Year of publication	Total no of cases (N)	Prognostic factors	P
1. Paesmans M et al.[7]	1995	1052	Age>60	.02
			Male	0.03
			Poor PS€	.0003
			Metastasis	<.0001
2. Martins SJ et al. [4]	1999	1635	Weight loss	<.0001
			SVCO	<.0001
			Poor PS€	<.0001
			Multiple Metastasis	<.0001
3. Brundage MD et al. [8]	2002	886	Stage IV	<.0001
			Multiple Metastasis	<.0001
			SVCO	<.0001
			Hypercalcemia	<.0001
			Raised LDH	<.0001
			Hypoalbuminemia	<.0001
4. Ademuyiva FO et al. [5]	2007	203	FEV1>2L*	0.014
			Higher Hb values *	0.007
5. Tibaldi C et al. [12]	2008	320	Squamous histology	<.0001
			Contralateral lung metastases	<.0001
			Raised WBC counts	<.0001
6. Wheatley-Price P et al. [10]	2010	2349	Female	0.002
			Adenocarcinoma	0.006
7. Tanriverdi O et al. [11]	2014	384	Serum uric acid (>7.49 mg/dL)	<.0001
			PS>2	<.0001
8. Berardi R et al. [13]	2016	401	Stage IVCancer	<.0001
			Wild type EGFR status	<.0001
			NLR≥3.7	<.0001
9. Li J et al. [14]	2019	8294	Liver metastases	<.0001
10. Lara van M at al. [15]	2020	1595	Larger tumour size	<.0001
			Higher Nodal stage	<.0001

Table 1: *€=Karnofsky performance (PS) status less than 60; *= Good prognostic factor; SVCO= Superior vena cava obstruction, FEV1= Forced expiratory volume in one second; Hb= Hemoglobin, WBC= White blood cell counts; NLR= Neutrophils to lymphocytes ratio.*

Discussion

HLung cancer is the most common cancer among males in India, with high mortality [2]. The initially asymptomatic course and lack of reliable screening methods lead to delay in diagnosis with the result that most of the patients present in the advanced stages of the disease. Many international studies have yielded variable results in prognostic factors that predict treatment outcomes in these patients.

In a study, 1,052 eligible patients with advanced non-small-cell lung cancer registered onto one of seven trials conducted by the European Lung Cancer Working Party (ELCWP) were enrolled to determine the prognostic value for survival of various pretreatment characteristics in patients with non-resectable non-small-cell lung cancer. They prospectively collected 23 variables and found that disease extent, Karnofsky performance status, WBC and neutrophil counts, metastatic involvement of skin, serum calcium level, age, and sex were significant prognostic factors for survival [7].

In 2007, a study was conducted on 203 patients with NSCLC

who were enrolled in a phase III trial conducted by the Hoosier Oncology Group and US Oncology between 2002 and 2006. Eligible patients had untreated stage III NSCLC, forced expiratory volume in one second (FEV1) ≥ 1 liter, baseline performance status of 0/1, and weight loss < 5% in 3 months preceding the trial. Univariate analysis, Cox proportional hazards regression, and parametric accelerated failure time models were performed to identify the factors that affected survival duration.

Variables analyzed included age (< 70 years vs. ≥ 70 years), sex, ethnicity, body mass index, performance status (0 vs. 1), FEV1 (> 2 L vs. 1-2 L), smoking status (current vs. never/former), hemoglobin (Hb) level, use of positron emission tomography scan in staging, and stage (IIIA vs. IIIB). The univariate analysis showed that Hb levels ≥ 12 were associated with improved survival (P = .033).

This analysis suggests that FEV1 > 2 L and higher pretreatment Hb values are associated with improved OS in patients with stage III NSCLC [5].

In 2008, a study conducted on 320 NSCLC patients found that squamous histology, number of metastatic sites >2, presence of bone, brain, liver, and contralateral lung metastases, and elevated leukocyte count in peripheral blood were all statistically significant prognostic factors in univariate analyses. In contrast, the other tested variables (sex, stage, age, presence of adrenal gland, and skin metastases) were not. Subsequently, a multivariate Cox's regression analysis identified PS 2 (P < 0.001, hazard ratio 2.57), elevated leukocyte count (P < 0.001, hazard ratio 1.79), squamous histology (P = 0.005, hazard ratio 1.45), and presence of brain metastases as independent prognostic factors for poor survival. Leukocyte count was a more decisive factor after performance status [12].

In 2010, a retrospective analysis of pooled data from five randomized, phase III of advanced NSCLC was done to investigate the role of sex and histology on efficacy, toxicity, and dose delivery after chemotherapy was given. Of 2349 patients, 34% were women. Women had a higher response rate to chemotherapy (42% versus 40%, P = 0.01) and longer survival than men (median OS 9.6 versus 8.6 months, P = 0.002). The difference in OS remained after adjusting for age, stage, performance status, and histology (hazard ratio 0.83, 95% confidence interval 0.74-0.92, P = 0.0005). Upon further examination, longer survival in women was only seen in patients with adenocarcinoma (test for interaction P = 0.006) [10].

In 2014 a study on 384 NSCLC patients investigated whether uric acid, the final breakdown product of purine metabolism in humans, has a prognostic significance in advanced NSCLC. Date of diagnosis, age, gender, performance status, smoking habit, weight loss within the past three years, disease stage, histological type of tumor, tumor diameter, area(s) of metastasis, number of metastasis, and the first-line treatment regimen of all patients were recorded. Serum uric acid levels were measured before first-line chemotherapy. Multivariate analysis showed that serum uric acid level (7.49 mg/dL) and poor performance status were independent prognostic factors (HR 3.18 95 % CI 1.36–6.41 and HR 2.18 95 % CI 1.18–3.21, respectively [11].

Another study was done to assess the prognostic role of neutrophilia, lymphocytopenia, and the neutrophil-to-lymphocyte ratio (NLR), in patients receiving first-line chemo- or targeted therapy for advanced non-small-cell lung cancer (NSCLC). They retrospectively analyzed 401 consecutive patients with advanced NSCLC treated with first-line chemo- or targeted therapy. Patients were stratified into two groups with pretreatment NLR ≥ 3.7 (Group A) vs. < 3.7 (Group B). The best NLR cut-off was identified by ROC curve analysis. A multivariate analysis, ECOG-PS≥2, stage IV cancer, non-adenocarcinoma histology, EGFR wild-type status, and NLR were predictors of worse OS. Stage IV cancer, wild type EGFR status, and NLR≥3.7 were independent prognostic factors for worse PFS.13

In conclusion, male gender, poor Karnofsky performance status, age>70 years, low pretreatment Hb, Serum albumin levels, high NLR ≥ 3.7, high baseline serum uric acid level (>7.49 mg/dL), stage IV cancer, EGFR wild-type status, and squamous histology and presence of brain metastases are predictors of worse OS. Hence, this subset of patients should be counseled regarding the disease outcomes and offer the best palliative care, especially in resource-poor countries, to reduce the financial and over- investigation-related burden for such patients and their relatives."

Conclusion

Hepato-cutaneous fistula is an uncommon complication after percutaneous pigtail drainage of liver abscess. Most of the cases can be managed conservatively, however some patients may require formal surgical excision of the tract.

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