Lung Cancer 137 (2019) 48–51

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Homologous recombination in lung cancer, germline and somatic mutations, clinical and phenotype characterization

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ARTICLE INFO

Keywords:
BRCA1
BRCA2
PALB2
Lung cancer
Homologous recombination
Platinum
PARP

ABSTRACT

Objectives: Identifying new predictive biomarkers in lung cancer that will prolong survival for additional subgroups of patients is of utmost importance. We report response to treatment and survival among homologous recombination deficient (HRD) lung cancer patients mostly BRCA mutation carriers to better define the predictive value of HRD status among non-small cell lung cancer (NSCLC).

Methods: We retrospectively evaluated our genetic and pathology database and identified 14 carriers of germline mutation in BRCA1 (n = 5), BRCA2 (n = 8), or PALB2 (n = 1) and a patient with a somatic BRCA2 mutation. Platinum compounds were part of the initial or follow-on treatment protocols in 9/11 with metastatic disease. Overall survival (OS) and response to platinum were analyzed in these patients.

Results: Median OS for the 11 patients was 30 months. The 2- and 3-year survival rates in our cohort were 62.5% and 28.6%, respectively, and 7/10 patients with metastatic lung cancer survived for more than 1 year which compares favorably with the literature. Of eight patients who were treated with platinum compounds, seven responded; however, in two the response endured for < 6 months. The Foundation Medicine LOH/HRD genomic score was calculated in three patients and the level was high in 2/3 (66%), including 1/2 tumors in germline BRCA mutation carriers and tumor in the patient with a somatic BRCA2 mutation. In both complete response to platinum was recorded.

Conclusion: Response rate to platinum compounds and survival in these patients do suggest that platinum-based therapies should still be incorporated in our treatment regimen for the patients with HRD lung cancer, and that BRCA and other HRR associated gene testing may be important in lung cancer patients.

1. Introduction

Lung cancer is the leading cause of cancer mortality among men and second to breast cancer among women. Up to 85–90% of cases are attributed to cigarette smoking. Around 85% of patients are diagnosed with non-small cell lung carcinoma (NSCLC), with approximately 80% diagnosed at stages III and IV. Median survival of patients treated with numerous combination chemotherapies has been around 1 year, with very few patients surviving more than 3 years after diagnosis. Targeted therapies have changed the prognosis for a select group of patients who harbor a tumor-specific oncogene that could be targeted. Immunotherapies are the latest addition to our arsenal of systemic treatments, but even these therapies are currently of limited value to most lung cancer patients.

It is of outmost importance to identify new predictive markers in lung cancer that will lead to effective treatment to significantly prolong survival for additional subgroups of patients. Assessing for germline or somatic BRCA status is already indicated for treatment decisions among ovarian cancer (OC) and breast cancer (BC) patients. Several studies reported high response to cisplatinum, an interstrand cross-linking agent that induces double strand breaks, in BRCA carriers with breast cancer [1]. Poly (ADP-ribose) polymerase-1 (PARP1) inhibitors entered the clinic for ovarian cancer based on several pivotal trials [2,3]. Importantly, carriers of somatic BRCA mutations and those whose tumors exhibited homologous recombination deficient (HRD) features had significantly better progression-free survival compared to patients

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https://doi.org/10.1016/j.lungcan.2019.09.008
Received 13 August 2019; Accepted 12 September 2019

whose tumors had an intact homologous recombination repair (HRR) mechanism. The search for a reliable biomarker for HRD is ongoing.

Cisplatinum doublets were once used as first-line therapy in all patients with NSCLC; however, this has changed dramatically in the last decade. Patients with driver DNA aberrations, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) among others, are treated with targeted therapies. In the rest of the NSCLC population, immunotherapy has to be incorporated as a single agent for patients with high programmed death ligand 1 (PDL1) expression or in combination with chemotherapy in patients with lower PDL1 levels. Interestingly, recently KEYNOTE 042 study found that even in patients with low PDL-1 levels, pembrolizumab treatment alone was better than chemotherapy [4]. Nevertheless, only a small minority of patients with lung cancer achieve complete response and are cured of their disease.

Due to the high prevalence of BRCA mutations in the Ashkenazi Israeli population, we have performed BRCA testing for many of our lung cancer patients, and in recent years next-generation sequencing panels for both germline and tumor DNA have included BRCA mutation testing. Here we report on the clinical history of NSCLC patients carrying mutations in genes that participate in HR DNA repair, BRCA, and PALB2, primarily germline mutations. We report impressive responses to platinum-based therapy in some of these patients, suggesting evaluation for HRD could play a role in treatment decisions for lung cancer patients.

2. Methods

2.1. Population

We retrospectively evaluated our clinical genetic and pathology data bases to identify all patients with NSCLC who underwent genetic evaluation from 1994–2018. Patients were tested based on their personal or family history, either through the Oncology Department or the Cancer Genetic Clinic of the Hadassah-Hebrew University Medical Center in Jerusalem, Israel. All patients were tested for the mutations known to have high prevalence among Ashkenazi Jews (BRCA1-c.68_69delAG, c.5266dupC, BRCA2-c.5946delT) and/or other common mutations in the non-Ashkenazi Jewish population (BRCA1-c.224-227delAAAG, BRCA2 c.7007 G > C among others). In recent years, some lung cancer patients have been evaluated with commercially available cancer gene panels and they were also identified. We also reviewed all patients who underwent tumor DNA genomic testing using Foundation Medicine to identify somatic mutation carriers of BRCA1/2 mutations. The FoundationOne LOH/HRD genomic score was calculated in selected mutation carriers, as previously described [2].

All patients who underwent genetic testing signed an informed consent form approved by the Medical Center's Institutional Review Board.

In the current study, we included all patients with NSCLC in whom a germline or somatic mutation in HRR associated genes, especially BRCA genes, was detected during a test for a specific mutation or gene panel screening.

Data regarding clinical characteristics, family history, histopathology, treatments administered, and disease outcome were retrospectively retrieved from medical files.

Treatment protocols varied significantly during the study period; therefore, we focus on platinum treatment and response and report on overall survival, however comparison to a matched control group is not possible.

3. Results

A total of 248 patients with lung cancer were evaluated for BRCA germline mutations and an additional nine patients underwent cancer gene germline panel testing as part of their clinical evaluation for treatment purpose. This highly selected population of lung cancer patients, more than half women, 46 with a history of BC and the majority with genetic testing limited to known and common BRCA mutations does not allow estimation of genetic predisposition to lung cancer in the general population.

Table 1
Clinical characteristics of lung cancer in patients with mutation homologous recombination related genes; BRCA and PALB2 mutation carriers identified from a population of 248 lung cancer patients evaluated for genetic predisposition.

Clinical parameters	Carriers of mutations in HRD related genes
Germline mutation carriers (n = 14)	
Male	5
Female	9
Age median (range)	69 (50-77)
Origin	
Ashkenazi	10
Non-Ashkenazi	4
Smoking Status	
Yes (former or current)	6
Never	6
Unknown	1
Stage	
I	4 (4 female, in 3 prior or concurrent BC diagnosis)
III	1
IV	9
Pathology	
Adenocarcinoma	13
Squamous cell carcinoma	1 (2 primaries in a patient)
Other malignancy	7
Breast cancer	5
Prostate cancer	2
Germline mutation	
BRCA1	5
185delAG	2
5382insC	2
Exon 6 delCTTT	1
BRCA2	8
6174delT	7
IVS2 + G > A	1
PALB2 (c.917A > T)	1
FoundationOne LOH/HRD score (n = 2) -BRCA1, 20/high, respone-CR > 5 years -BRCA2, 7/low, no platinum treatment)	
Somatic mutation carriers (n = 1)	
BRCA2 E537*, smoker, Stage IV LOH/HRD score 24/high, response-CR	
EGFR mutation in germline (11) and somatic (1) mutation carriers (unknown in 4)	04-Dec

Among the 257 lung cancer patients, 14 (5.5%) were found to carry a germline homologous recombination repair (HRR) mutation in a cancer predisposing gene. These included germline BRCA mutations in 13 patients–BRCA1 in five (c.68_69delAG in two, c.5266dupC in two, c.224-227delAAAG in one), BRCA2 in eight (6175delT in seven, c.7007 G > C in one), and a PALB2 mutation (c.917A > T) in one patient. The PALB2 mutation was identified using a cancer gene panel in a patient who was also diagnosed with BC and had a significant family history. One additional patient was found to carry a likely somatic BRCA2 (E537*) mutation when a FoundationOne genomic test was performed as part of his clinical evaluation.

The clinico-pathological characteristics of these 15 patients Table 1. Among 14 germline mutation carriers, the median age at lung cancer diagnosis was 69 years (range 50–77). Eight of the patients were female (57.1%). Among germline mutation carriers, 6/14 (43%) were former or current smokers. All 10 Ashkenazi and three non-Ashkenazi Jewish patients were carriers of one of the known BRCA Jewish founder mutations. Other malignancies were found in 7/15 patients (47%); five

patients had BC (two bilaterally), and two patients had prostate cancer.

All of the patients had adenocarcinoma of the lung with one female with history of smoking who had both a primary lung adenocarcinoma and a primary squamous cell lung carcinoma. The EGFR mutation was found in 4/11 tumors that were tested, including the patient with a wild-type [WT] somatic BRCA mutation. Six patients were tested for other genetic changes that are relevant to lung cancer (ALK, ROS), and all the tumors were WT. The Foundation Medicine LOH/HRD genomic score was calculated in three patients and the level was high in 2/3 (66%), including 1/2 tumors in germline BRCA mutation carriers and tumor in the patient with a somatic BRCA2 mutation.

Four patients with early stage disease, all women, were diagnosed with lung cancer after or concurrently with a diagnosis of early-stage BC as part of evaluation due to BC diagnosis without a history of chest wall irradiation in any of them. These patients underwent surgery and did not receive any adjuvant treatment for lung cancer. All are with no evidence of disease at a mean of 8 years (range 1–15) of follow up.

Survival of the 10 patients with metastatic disease and one patient with locally advanced disease at diagnosis (nine with BRCA germline mutations, one with a PALB2 germline mutation, and one with a somatic BRCA mutation) is presented in the Fig. 1. Platinum compounds were part of the initial or follow-on treatment protocols in 9/11. Patients with metastatic disease were also treated with other chemotherapy agents, immunotherapy and anti-EGFR treatment in those with EGFR mutations. Median overall survival for the 11 patients was 30 months. The 2- and 3-year survival rates in our cohort were 62.5% and 28.6%, respectively, and 8/10 patients with metastatic lung cancer survived for more than 1 year. Five patients were alive and continuing treatment at data cutoff, at 6, 11, 12, 23, and 61 months from diagnosis.

Of eight patients who were treated with platinum compounds, seven responded; however, in two the response endured for < 6 months. Platinum compounds were administered to 2/3 patients in which a FoundationOne LOH/HRD score was available. The duration of response for two with high HRD/LOH scores were 23 and 61 months while the patient with low HRD/LOH score did not receive platinum.

It should be noted, however, that these patients were treated over a period spanning > 20 years. Treatment paradigms completely changed in this period, which precluded matching a comparable control group.

4. Discussion

Lung cancer is mainly attributed to environmental exposures, especially cigarette smoking, while the contribution of high penetrance genetic predisposition to lung cancer is largely unknown.

Lung cancer is not considered a part of the BRCA syndrome. In large cohorts of BRCA carrier kindred, risk for lung cancer was not elevated [5]. An analysis of 555 adenocarcinoma lung cancer patients from The Cancer Genome Atlas (TCGA) [6] found that 2.5% were carriers of a pathogenic mutation in DNA repair genes (ATM, BRCA2, CHECK2, PARK2, TERT, TP53, YAP1), and additional 2% were carriers of ultra-

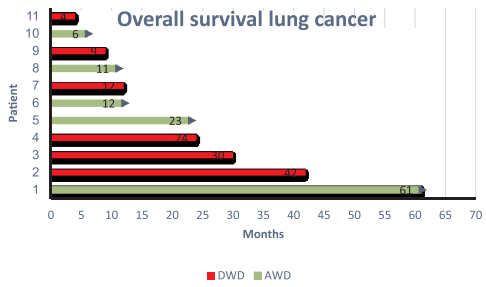

Fig. 1. Overall survival of 11 patients with adenocarcinoma of the lung at stage IV (n = 10) and IIIb (n = 1) carriers of germline BRCA1, BRCA2 and PALB2 and a patients with somatic BRCA1 mutation.
Abbreviations: DWD died with disease. AWD alive with disease

rare variants which translates to an odds ratio (OR) for lung adenocarcinoma of 66 (95% confidence interval: 33–125) in mutation carriers, suggesting a subset of lung cancer patients with inherited susceptibility. However, only one BRCA2 mutation carrier was identified, and BRCA1, PALB2, and other genes involved in HR DNA repair were not included in the analyses. In a previous study Among 110 lung cancer patients of Ashkenazi Jewish origin, three carriers of BRCA1/2 founder mutations were identified (2.7%), a frequency that is similar to the 2.5% expected in the Ashkenazi general population [7].

Nevertheless, we identified 14 lung cancer patients who were carriers of a germline mutation in BRCA1 (n = 5), BRCA2 (n = 8), or PALB2 (n = 1) and one patient with a somatic BRCA2 mutation. Our biased population precludes estimation of genetic predisposition to lung cancer in the general population. Our lung cancer patients carrying BRCA mutations included a high proportion of women (57.1%) and nonsmokers (60%). Our series does not support smoking as a synergistic risk factor with BRCA germline mutation status, and follow-up for carrier smokers should be similar to the guidelines in the general population with smoking history.

The search for a reliable biomarker for HRD is still ongoing. If the development of lung cancer in BRCA carriers is not related to the mutation, the tumor phenotype may be similar to sporadic tumors and will not necessarily exhibit a high HRD score. Only three patients in our series were evaluated by the FoundationOne genomic test for HRD score. A high LOH/HRD score was found in two of them (1/2 germline BRCA carriers and in the one somatic BRCA mutated tumor). The frequency of high LOH/HRD scores in sporadic lung adenocarcinoma is unknown; however, in one of our patients with BRCA2 germline mutation the HRD score in the tumor was low.

This score was used in ARIEL studies of rucaparib in ovarian cancer [2] and correlated with better response to rucaparib in BRCA WT tumors with a high LOH/HRD score. Study 19 of olaparib in OC patients [3] used a test based on HRD-loss of heterozygosity (LOH), HRD-telomeric allelic imbalance (TAI), and HRD-large-scale stage transitions (LST). In breast cancer patients, these HRD scores correlated with BRCA1/2 deficient tumors suggesting that these scores may effectively capture HRD tumors regardless of BRCA status [8].

Response to platinum is a clinical predictor of HRD score among OC and BC patients [1–3]. We observed response to cisplatinum in 7/8 of the patients treated with platinum compounds for metastatic disease, with long responses of more than a year in six of them (75%) and 2 year survival of 62.5%. This compares favorably with a 19–30% response rate with doublet therapy [9,10], where there was 1-year survival of 33%–43%, and 2-year survival of 11%–18.9% respectively. Interestingly, an exceptionally long response was recorded in a BRCA1 germline mutation carrier with a high LOH/HRD score who had a complete response to treatment with platinum compounds. When platinum was omitted from the regimen due to toxicity there was disease progression, with immediate response after platinum treatment was resumed, which has been sustained for 58 months and switched to PARPi treatment for 6 months now.

In conclusion, our findings are based on a small and highly selected sample, and should be carefully interpreted. With these reservations, high and long responses to platinum compounds were observed in this cohort of metastatic lung cancer patients carrying germline or somatic mutations in HRR genes, especially in the BRCA1/2 genes. BRCA1/2 carrier status, either germline or somatic, correlated with high LOH/HRD score in 2/3 of the evaluable tumors. Our results are of special interest in light of the recent results of phase 3 studies suggesting that for a large fraction of patients, immunotherapy alone might turn out to be more efficacious than chemotherapy, prompting physicians to avoid the use of chemotherapies in a significant percentage of patients due to toxicity. Therefore, addition of HRD testing may contribute to better identification of platinum-sensitive patients that may benefit from platinum or alternatively PARP inhibitors, as an important component of the therapy in addition to immunotherapies. The addition of PARP

inhibitors to the armamentarium of treatments in HRD lung cancers may produce long-term responses in this subgroup of lung cancer patients.

Luna Kadouri: Receipt of research support: investigator in clinical trials (institutional support for clinical trials) sponsored by Novartis, Bayer, Eli Lilly, AstraZeneca, Abbvie, MSD. Roche

Yakir Rottenberg: Receipt of research support: investigator in clinical trials (institutional support for clinical trials) sponsored by MSD, AstraZeneca, Janssen. Roche

Aviad Zik: Grant from Merck Serono Ltd.

Doron Lipson: Employee of Foundation Medicine Inc. Cambridge, MA

Tamar Peretz: Consultation fees and Talks in a company's organized events: Roche, Pfizer, Neopharm, MSD, AstraZeneca, Jansen, Teva Pharmaceuticals, Medison

Receipt of research support: investigator in clinical trials (institutional support for clinical trials) sponsored by MSD, Roche, Novartis, Bayer, Eli Lilly, AstraZeneca, Abbvie, Bayer, Daiichi Sankyo, Radius, Puma, Cascadian Therapeutics

Hovav Nechushtan: Receipt of research support: investigator in clinical trials (institutional support for clinical trials) sponsored by MSD, Clovis, AstraZeneca, Merck Serono

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or non-for-profit sectors.

Non Financial support: HRD/LOH score was calculated by Foundation Medicine for 3 of the patients that performed the test previously for clinical purposes.

Declaration of Competing Interest

Tamar Hamburger declares no conflicts of interests.

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