BRIEF REPORT

Brief Report: Real-World Eligibility for Clinical Trials in Patients With Extensive-Stage SCLC at a Tertiary Care Center

Navdeep Dehar, M.B.B.S., MD, MBT, FRCPC,[a,b] Mahbuba Meem, MD,[a,b] Ishita Aggarwal, MD, MPH,[a,b] Wilma Hopman, MA,[a] Pierre-Olivier Gaudreau, MD, PhD, MPs, FRCPC,[a,b] Andrew Robinson, MD, MSc, FRCPC,[a,b] Andrea S. Fung, MD, PhD[a,b,*]

[a]*Department of Oncology, Queen's School of Medicine, Queen's University, Kingston, Ontario, Canada*
[b]*Cancer Centre of Southeastern Ontario, Kingston Health Sciences Centre, Kingston, Ontario, Canada*

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ABSTRACT

Introduction: The CASPIAN and IMpower133 trials revealed a significant survival benefit of chemotherapy plus immunotherapy in patients with extensive-stage SCLC. The current study characterizes the proportion of real-world patients who would have met eligibility for these trials and highlights factors influencing eligibility in the real-world setting.

Methods: A retrospective analysis of patient data was conducted for stage IV patients with SCLC treated at the Cancer Centre of Southeastern Ontario, Canada. Trial eligibility was based on criteria used in the IMpower133 and CASPIAN trials. Data were summarized using descriptive statistics. Overall survival was assessed using the Kaplan–Meier method.

Results: Of the 116 patients included, only 12.1% met the overall eligibility criteria for the IMpower133 trial, and 14.7% for the CASPIAN trial. The most common reasons for ineligibility included: Eastern Cooperative Oncology Group (ECOG) 2 or greater (77.5%), inadequate organ function (48%), and the presence of brain metastases at diagnosis (37.3%). Sixty-one patients (59.8%) met two or more major ineligibility criteria. If trial eligibility was expanded to include ECOG 2 patients, an additional 10.3% would have met eligibility. The median overall survival for all-comers was 6.5 months.

Conclusions: Only a small minority of real-world patients with extensive-stage SCLC would have met eligibility for the IMpower133 and CASPIAN trials, with ECOG greater than or equal to 2, inadequate organ function, and brain metastases comprising the most common reasons for trial ineligibility. Future clinical trials should expand the inclusion criteria to better represent real-world patient populations.

Keywords: SCLC; Real world; Clinical trial eligibility; IMpower133; CASPIAN

Introduction

Platinum-etoposide chemotherapy has been the mainstay of first-line treatment of extensive-stage SCLC (ES-SCLC) for many years. However, a small survival benefit of approximately 2 months was shown with the addition of atezolizumab or durvalumab immunotherapy to platinum-etoposide chemotherapy compared with chemotherapy alone in the IMpower133[1,2] and CASPIAN trials,[3,4] respectively. Despite initial response to therapy, patients often recur with limited treatment options available in subsequent lines. Therefore, there remains a

*Corresponding author.
Address for correspondence: Andrea S. Fung, MD, PhD, Cancer Centre of Southeastern Ontario, Burr 2, 25 King Street West, Kingston, Ontario, K7L 5P9, Canada. E-mail: andrea.fung@ahs.ca

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need for novel therapeutic strategies for the treatment of patients with ES-SCLC.

Patients with ES-SCLC are often symptomatic with significant disease burden at the time of diagnosis. The disease progresses rapidly and can worsen clinical symptoms, thereby limiting the time a patient can wait for treatment initiation and making recruitment to clinical trials challenging in clinical practice. The strict eligibility criteria and additional investigations required for randomized trials may limit the proportion of patients who can be enrolled, eventually impacting the generalizability of trial results to real-world patient populations.[5–7]

The current study aims to determine the proportion of patients at the Cancer Centre of Southeastern Ontario who would have met clinical trial eligibility on the basis of the criteria used in the IMpower133 and CASPIAN trials and to evaluate which factors might impact trial enrollment in a real-world setting.

Materials and Methods

A retrospective chart review was conducted for all stage IV patients with SCLC treated at the Cancer Centre of Southeastern Ontario (Kingston, Ontario, Canada) between January 1, 2016, to December 31, 2020. Patient demographics, pathologic, treatment, toxicity, and outcome data were collected. Patients were categorized as eligible or ineligible on the basis of key eligibility criteria utilized in the IMpower133 and CASPIAN clinical trials (Supplementary Table 1). The study was approved by the Queen's University research ethics board and a waiver of informed consent was approved for retrospective chart review.

The primary outcome was to determine the proportion of patients who would meet the key eligibility criteria utilized in the CASPIAN or IMpower133 trials and to characterize the reasons for ineligibility in a real-world patient population. The proportion of patients who would be eligible if eligibility criteria were expanded to include Eastern Cooperative Oncology Group (ECOG) 2 performance status or with assessment after one cycle of systemic therapy was determined. The median time from diagnosis to oncology consult and diagnosis to treatment was evaluated. The date of diagnosis was defined as the date of pathologic diagnosis. Overall survival (OS) was defined as the date of diagnosis to the date of death or date of last follow-up.

Clinical characteristics and trial eligibility were summarized using descriptive statistics. The underlying distribution of continuous data was assessed with the Shapiro–Wilk test. Kaplan–Meier curves were generated to compare OS for chemotherapy status, and statistical significance was assessed using the Log-Rank test. A p value of less than 0.05 was considered statistically significant, and no adjustment was made for multiple comparisons. IBM SPSS (version 28.0 for Windows, Armonk, NY) was used for statistical analysis.

Results

Patient Characteristics

The study included 116 patients with a mean age of 70 years. Baseline patient characteristics are summarized in Table 1. Most patients (94.8%, n = 110) were current or former smokers. Thirty-seven patients (31.9%) were ECOG 0 to 1 at diagnosis, 27.6% (n = 32) ECOG 2, and 40.5% (n = 47) ECOG 3 to 4. Forty-three patients (37.1%) had brain metastases at diagnosis, while 55.2% (n = 64) had liver metastases.

With respect to treatment, 57.8% (n = 67) received chemotherapy and 10.3% (n = 12) had chemoimmunotherapy. Forty-nine patients (62.0%) completed four to six cycles of chemotherapy, whereas 25.3% (n = 20) only received one cycle. The most common reasons for discontinuation of first-line chemotherapy were functional decline (10.1%, n = 8) and toxicity (10.1%, n = 8). Of the evaluable patients who received first-line systemic therapy, 51 (81.0%) progressed. However, only

Table 1. Baseline Characteristics of Study Patients

Total Patients (N = 116)	n (%)
Mean age at diagnosis	70 ± 9
ECOG	
0	6 (5.2)
1	31 (26.7)
2	32 (27.6)
3	37 (31.9)
4	10 (8.6)
Smoking status	
Former	55 (47.4)
Current	55 (47.4)
Never-smoker	4 (3.4)
Unknown	2 (1.7)
Metastasis at diagnosis	
Liver	64 (55.2)
Brain	43 (37.1)
Chemotherapy	
Yes	67 (57.8)
No	37 (31.9)
Chemoimmunotherapy	12 (10.3)
Prophylactic cranial irradiation (Total N = 73)	
Yes	9 (12.3)
No	63 (86.3)
Unknown	1 (1.4)
Consolidative thoracic radiation	
Yes	20 (17.2)
No	95 (81.9)
Unknown	1 (0.9)

ECOG, Eastern Cooperative Oncology Group.

a quarter (24.4%, n = 19) received second-line systemic treatment. Only 12.3% (n = 9 of 73) of patients without baseline brain metastases received prophylactic cranial irradiation. Twenty patients (17.2%) received consolidative radiation to the chest.

Trial Eligibility

Only 12.1% (n = 14 of 116) of patients met the overall eligibility criteria for the IMpower133 trial and 14.7% (n = 17 of 116) for the CASPIAN trial. The higher proportion of eligible patients for the CASPIAN trial compared with IMpower133 was due to less strict eligibility criteria for patients with brain metastases.

The common reasons for ineligibility included: ECOG 2 or greater (77.5%, n = 79 of 102), inadequate hematologic or end-organ function (48.0%, n = 49 of 102), presence of symptomatic or untreated brain metastases at diagnosis (37.3%, n = 38 of 102) and comorbidities (7.8%, n = 8 of 102) (Fig. 1*A*). Forty-eight patients (47.1%) met two ineligibility criteria, and 12.7% (n = 13) met three or more (Supplementary Table 2).

If trial eligibility was expanded to include ECOG 2 patients at baseline, an additional 10.3% (n = 12) would have met eligibility. If patients were ineligible at baseline but were evaluated for eligibility after receiving one cycle of systemic therapy, an additional 14.7% (n = 17) patients would have become eligible (Fig. 1*B*).

Time from Diagnosis to Treatment and Survival data

In the current patient population, the median time from diagnosis to medical oncology consult was seven days. The median time from consult to treatment was five days and the time from diagnosis to treatment

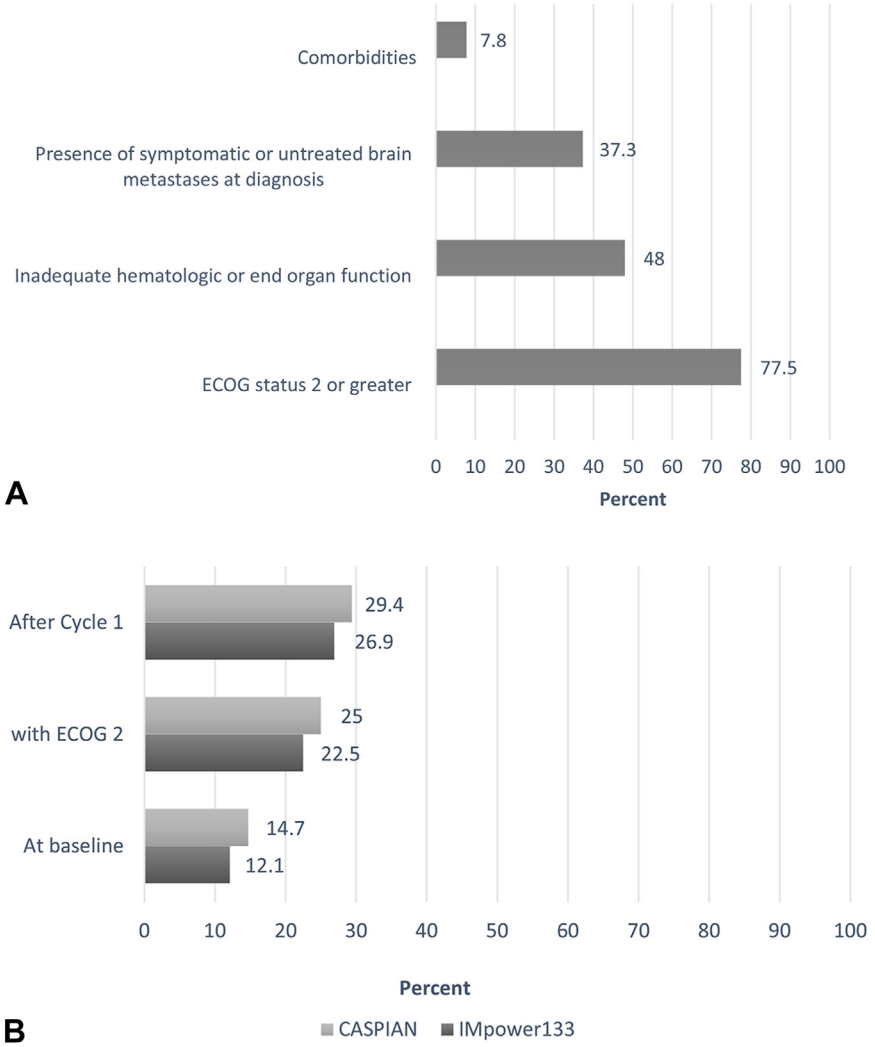

Figure 1. (*A*) Reasons for trial ineligibility at baseline. (*B*) Percentage of patients eligible for the IMpower133 (dark gray) and CASPIAN (light gray) trials if eligibility criteria were expanded to include ECOG 2 patients, or if patients were assessed after cycle 1 of systemic therapy. ECOG, Eastern Cooperative Oncology Group.

initiation was 12 days. The median OS (mOS) for patients treated with chemotherapy was 6.5 months (95% confidence interval [CI]: 5.4–7.6) versus 0.9 months (95% CI: 0.5–1.3) for those who did not receive chemotherapy ($p < 0.001$; Fig. 2*A*). There was no significant difference in survival between trial eligible versus ineligible patients treated with chemotherapy (mOS 8.9 versus 6.3 mo, $p = 0.20$; Fig. 2*B*).

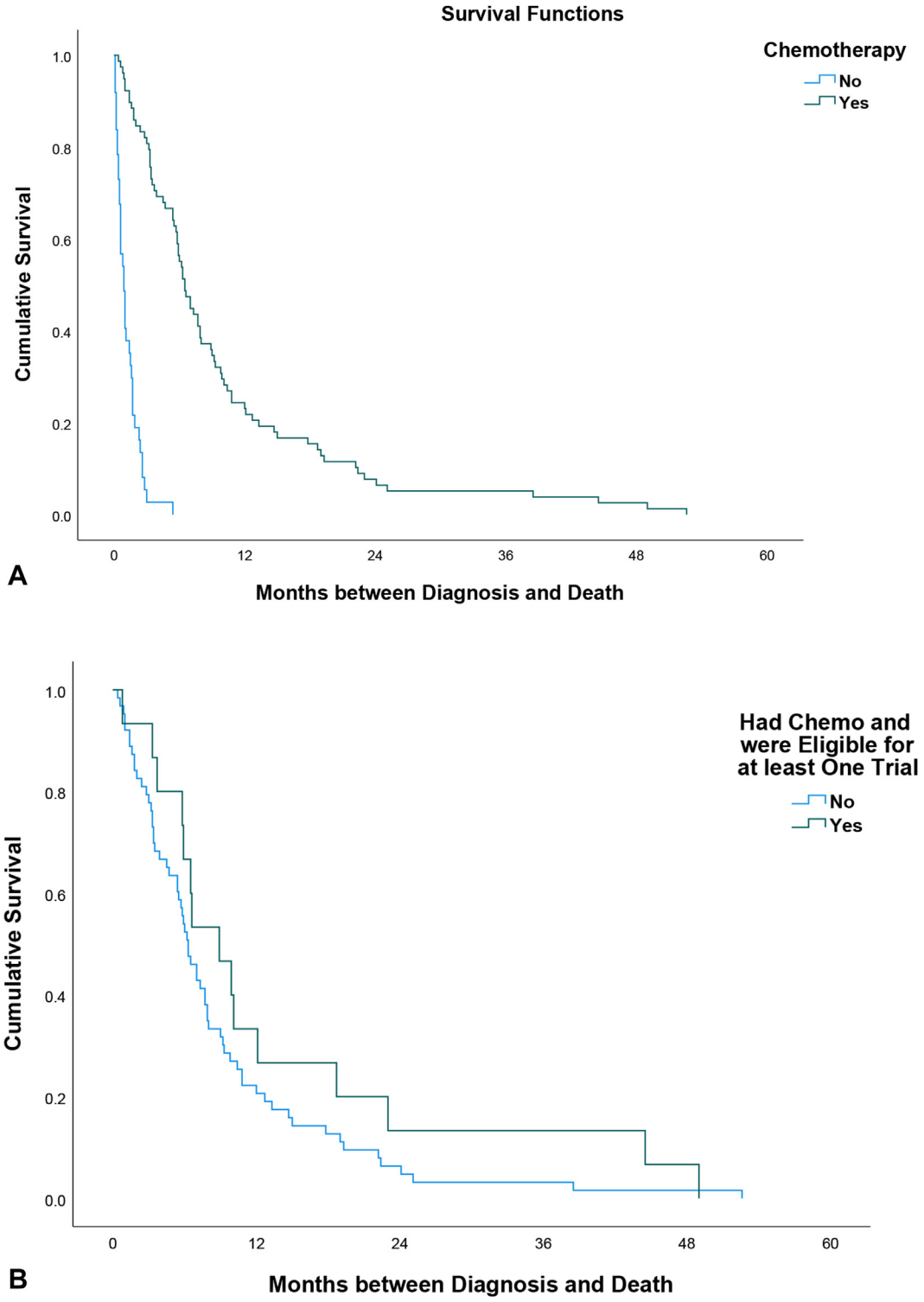

Figure 2. (*A*) Median overall survival of patients treated with chemotherapy (green) versus those who did not receive chemotherapy (blue). (*B*) Median overall survival for patients treated with chemotherapy who met eligibility for at least one clinical trial (green) compared to trial ineligible patients treated with chemotherapy (blue).

Discussion

There is limited data evaluating the impact of strict eligibility criteria on patient inclusion in clinical trials for patients with SCLC. Multiple organizations, including the American Society of Clinical Oncology, have made recommendations for broadening eligibility criteria in trials.[7–9] However, patients with ES-SCLC are a unique population, who are often symptomatic at presentation with substantial disease burden and rapidly progressive disease, which can make recruitment to clinical trials particularly challenging in clinical practice.

This study shows that only 12.1% of real-world stage IV patients with SCLC would have met the eligibility criteria for IMpower133 and 14.7% for CASPIAN. The most common reason for ineligibility was having a performance status of ECOG 2 or greater (77.5%). Despite the high percentage of patients with ES-SCLC presenting with higher ECOG status, this group has been excluded from most of the landmark clinical trials. In our study, 31.9% of patients were ECOG 0 to 1 at presentation, 27.6% ECOG 2, and 40.5% ECOG 3 to 4. If clinical trial eligibility were expanded to include ECOG 2, an additional 10.3% of patients in our study would have met eligibility. Similarly, Rittberg et al.[10] reported an additional 29% of patients with ES-SCLC in their study would have become eligible for chemoimmunotherapy if inclusion criteria were expanded to include ECOG 2.

In our study, patients had a median time from consult to treatment of 5 days, highlighting the challenges of trial accrual if multiple additional investigations are required for eligibility which could delay treatment initiation. Some patients with SCLC have an improvement in cancer-related symptoms or performance status after the first cycle of systemic treatment. Rittberg et al.[10] revealed that after one or two cycles of systemic therapy, an additional 7% and 4% of patients, respectively, had an improvement in performance status to ECOG 0 to 1. When we evaluated the proportion of patients that might be eligible by cycle 2, we found that an additional 14.7% (n = 17) of patients would have met eligibility criteria. These results provide meaningful insights into considerations for clinical trial design for patients with SCLC. In the CCTG IND.226 trial,[11] patients with SCLC could receive up to two cycles of standard chemotherapy before the addition of the experimental immune checkpoint inhibitor agent(s), thereby highlighting the feasibility of this approach.

The mOS of our population (6.5 mo, 95% CI: 5.4–7.6) was lower than the chemotherapy alone arm in the CASPIAN trial at 10.5 months[12] and IMpower133 trial at 10.3 months,[2] which reflects the differences between the clinical trial and real-world populations. Importantly, we found that there was no significant difference in survival between trial-eligible versus ineligible patients (mOS 8.9 versus 6.3 mo, $p = 0.20$; Fig. 1*B*) in our study. This suggests that patients seem to derive benefit from treatment, even if they might not meet the stringent criteria set out in clinical trials; therefore, consideration of expanding some eligibility criteria to better reflect real-world patient populations should be evaluated.

This study has limitations including a small sample size, being conducted at a single center, and the retrospective nature of the analysis. Only a few patients received chemoimmunotherapy during the study period as these regimens were not accessible in routine practice; therefore, we are unable to comment on the outcomes of patients treated with chemoimmunotherapy on the basis of trial eligibility.

Conclusions

In the current study, only a small minority of real-world patients with ES-SCLC would have met eligibility for the IMpower133 and CASPIAN trials. Expanding the eligibility criteria to include ECOG 2 patients or evaluating patients after one cycle of chemotherapy would have doubled the proportion of eligible patients. Future clinical trials should evaluate trial design and eligibility criteria to optimize the inclusion of patients with ES-SCLC to generate results more applicable to real-world patient populations.

CRediT Authorship Contribution Statement

Andrea S. Fung: Conceptualization, Methodology, Writing- review and editing

Andrew Robinson: Conceptualization, Writing-review and editing

Wilma Hopman: Methodology, Statistical analysis, Writing-original draft

Navdeep Dehar: Writing-original draft

Mahbuba Meem: Writing-original draft

Ishita Aggarwal: Writing-original draft

Pierre-Olivier Gaudreau: Writing- review and editing

Disclosure

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at [https://doi.org/10.1016/j.jtocrr.2024.100696].

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