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Health Care Resource Use Among Patients with Advanced Non–Small Cell Lung Cancer in Japan, 2017–2019

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ABSTRACT

Background: First-line immune checkpoint inhibitor (ICI) monotherapy for advanced non–small cell lung cancer (NSCLC) was introduced in Japan in February 2017. Limited information is available since that time regarding health care resource use for NSCLC in Japan, where the hospitalization burden is high.
Objective: We evaluated health care resource use from first- through third-line systemic anticancer therapy for patients with advanced NSCLC included in a multicenter, retrospective chart review study.
Methods: Eligible patients were aged 20 years or older with unresectable locally advanced/metastatic NSCLC with no known actionable genomic alteration who initiated first-line systemic anticancer therapy from July 1, 2017, to December 20, 2018, at 23 Japanese hospitals. We calculated the percentage of patients with a record of each resource used, the total number of each resource, and the resource use per 100 patient-weeks of follow-up from initiation of first-, second-, and third-line therapy, overall and by the 3 most common regimen categories, namely, ICI monotherapy, platinum-doublet chemotherapy (without concomitant ICI), and nonplatinum cytotoxic regimens (nonplatinum). Study follow-up ended September 30, 2019.
Results: Among 1208 patients (median age = 70 years; 975 [81%] men), 463 patients (38%) received ICI monotherapy, 647 (54%) received platinum-doublet chemotherapy, and 98 (8%) received nonplatinum regimens as first-line therapy. During the study, 621 (51%) patients initiated second-line, and 281 (23%) initiated third-line therapy. The majority of patients experienced ≥1 hospitalization (76%–94%) and ≥1 outpatient visit (85%–90%) during each therapy line. The number of hospitalizations increased from 6.5 per 100 patient-weeks in first-line to 8.0 per 100 patient-weeks in third-line. During first-line therapy, the number of hospitalizations per 100 patient-weeks were 4.8, 8.4, and 6.5 for patients receiving ICI monotherapy, platinum-doublet chemotherapy, and nonplatinum regimens, respectively, and the percentages of hospitalizations categorized as attributable to NSCLC treatment administration (no surgery, procedure, treatment of metastasis, or palliative lung radiation) were 64%, 77%, and 73%, respectively. The num-

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ber of outpatient visits increased from 43.0 per 100 patient-weeks in first-line to 51.4 per 100 patient-weeks in third-line therapy. During first-line therapy, outpatient visits per 100 patient-weeks were 41.0, 46.7, and 33.0 for patients receiving ICI monotherapy, platinum-doublet chemotherapy, and nonplatinum regimens, respectively, and the percentages of outpatient visits for infusion therapy were 48%, 34%, and 36%, respectively.

Conclusions: The results of this study, although solely descriptive, showed differing patterns of health care resource use during first-line therapy among the 3 common systemic anticancer therapy regimens for advanced NSCLC in Japan and suggest that further research is needed to investigate these apparent differences by treatment regimen.

Introduction

Incident cases of tracheal, bronchus, and lung cancer increased by 37% from 2007 to 2017 worldwide, largely because of aging populations and population growth.[1] In Japan, lung cancer is the number-1 cause of cancer-related death,[1–3] and the percentage of the population aged 65 years or older is the highest in the world, hitting 29% in 2021 and estimated to increase to 35% in 2040.[4] The aging of the population thus presents a burden on the health care system, reflected in estimates of national medical care expenditures for treating cancers, which have risen steadily each year from 2007 to 2019.[5] In 2021, the estimated annual cost of treating cancer in Japan was 40 billion Japanese yen.[6,7]

A universal health insurance system was established in Japan in the 1960s and covers the cost of most medical care. The ceiling for total out-of-pocket costs per month, including hospitalization costs, is determined based on household income and is an amount usually much lower than the price of newly approved anticancer drugs. This enables Japanese doctors to select the optimal cancer care for each individual, without patients being limited by financial burden. However, the financial burden falls on the payer, namely, the Japanese health insurance body and government.

Hospitalizations are a major cost driver, with the cost of inpatient care comprising 40% of total medical expenditures in Japan in fiscal year 2020,[8] and treatment of cancer often requires hospitalization. A recent study reported that, during 2017, lung cancer was associated with the highest per-patient cost and longest median duration of hospitalization during the first year after diagnosis among 5 common cancers in Japan, the others being stomach, colorectal, liver, and breast cancer.[7] Furthermore, a multinational study of health care resource use (HCRU) for advanced non–small cell lung cancer (NSCLC) during 2011 to 2016 found that hospitalizations for lung cancer in Japan were among the most frequent of 8 countries, with length of each hospital stay being the longest, relative to the other 7 countries (Italy, Spain, Germany, Australia, South Korea, Taiwan, and Brazil).[9] Indeed, as of the most recent country data (for 2020), Japan remains an outlier for longest average (all-cause) hospital stay of 16.4 days among those evaluated by the Organisation for Economic Co-operation and Development.[10] Although the economic burden of hospitalizations falls on the payer, frequent long hospitalizations can be associated with potential ill effects for caregivers and patients, including risks of hospital-related infections, reduced health-related quality of life, and loss of function with regard to the activities of daily living, especially because many patients with lung cancer are older.

New targeted therapies and immune checkpoint inhibitors (ICIs) have become available for treating lung cancer over the past 10 years, with the first ICI (nivolumab) approved for previously treated unresectable advanced/metastatic NSCLC during 2015. In February 2017, pembrolizumab became the first ICI approved and reimbursed in Japan as first-line monotherapy for unresectable advanced/metastatic NSCLC with programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥50%. Findings of a recent observational study indicate that there has been an improvement in real-world clinical outcomes of patients with advanced NSCLC in Japan since the introduction of first-line immunotherapy,[11] and results of a recent single-center study suggest that NSCLC treatment may be shifting from inpatient to outpatient settings in Japan.[12] However, HCRU for advanced NSCLC since 2017 in Japan has not yet been described in detail. Here we report HCRU by line of therapy and regimen type for patients with advanced NSCLC included in a multicenter retrospective study conducted after the introduction of first-line immunotherapy in Japan.

Patients and Methods

Patients and study design

This observational study was conducted using retrospective chart abstraction at 23 centers throughout Japan, as previously described in detail.[11] Both inpatient and outpatient care were available at these facilities and were captured via chart review. Eligible patients had unresectable locally advanced or metastatic NSCLC diagnosed at age 20 years or older, and they initiated first-line systemic anticancer therapy from July 1, 2017, to December 20, 2018, thus after the introduction of first-line ICI monotherapy and before the introduction of first-line ICI-chemotherapy combinations for advanced NSCLC (on December 21, 2018); follow-up was until September 30, 2019, inclusive. Results for PD-L1 TPS on or before the start of first-line therapy were required for inclusion. Key exclusion criteria were NSCLC with known actionable genomic aberration, receipt of first-line therapy in a clinical trial, and NSCLC that could be treated with curative intent through either surgical resection and/or concomitant chemoradiation.[11]

The protocol for this noninterventional study conformed to the provisions of the Declaration of Helsinki and was approved at each participating center by the local Ethics Committee, as previously reported.[11] Informed consent from individual patients was not required by the Ethics Committees, as per ethical guidelines of the Japan Ministry of Health Labour and Welfare.[13]

HCRU assessment and analyses

Study outcomes and analyses were prespecified in the statistical analysis plan.

We calculated the number and percentage of patients with a record of each type of health care resource used (eg, hospitalization and outpatient visits), the total number of each resource used, and the resource use per 100 patient-weeks of follow-up during first-, second-, and third-line therapy, overall and by the 3 most common regimen categories, namely, ICI monotherapy, platinum-doublet chemotherapy, and nonplatinum cytotoxic regimens. The

index date was defined for each line of therapy as the date of initiating systemic anticancer therapy. Use of each health care resource was assigned to a specific line of therapy based on the utilization dates.

Using descriptive statistics, we summarized hospitalizations, emergency department (ED) and intensive care unit (ICU) visits that were associated with hospitalizations, outpatient visits, radiation therapy, imaging tests, and laboratory testing. Hospitalizations were summarized for lung cancer overall and also specifically for hospitalizations attributable to NSCLC treatment administration. We defined the latter (hospitalizations for NSCLC treatment administration) as those for which the primary reason for admission was treatment of lung cancer (without surgery, procedures, treatment of metastasis, or palliative lung radiation). In Japan, hospitalizations are charged according to a national price-fixed payment system based on the primary reason for admission. The length of each hospital stay was calculated in days using the admission and discharge dates. Outpatient visits were summarized overall and by additional details (outpatient infusion center visit, imaging tests, and laboratory testing during the visit).

For each line of therapy, patient-weeks of follow-up were calculated for each patient as (start date of subsequent line of therapy [or end of follow-up if no subsequent line of therapy] – index date + 1) / 7. For continuous variables, descriptive statistics included the number of patients, mean (SD), median, range, and number of patients with missing data, as appropriate for each variable. Frequencies, percentages, and the number of missing data were displayed for categorical variables. Percentages were based on the number of nonmissing data as the denominator, unless otherwise specified. Handling of missing data has been previously described.[11]

Analyses were implemented using SAS software, version 9.4 or later (SAS Institute, Cary, North Carolina). No formal hypothesis was evaluated in this descriptive study, and all eligible patients were included; therefore, no a priori sample size calculations were performed.

Results

Patients and systemic anticancer regimens

The majority of the 1208 eligible patients with unresectable advanced/metastatic NSCLC were men (n = 975 [81%]), and median age was 70 years (range = 27–92 years), as previously described.[11] Among 1155 patients with known NSCLC histologic diagnosis, 712 patients (62%) had nonsquamous, 367 (32%) had squamous, and 76 (7%) had other NSCLC histology. A total of 463 patients (38%) received ICI monotherapy, 647 (54%) received platinum-doublet chemotherapy (without concomitant ICI), and 98 (8%) received a nonplatinum cytotoxic regimen as first-line therapy (Table 1).

Patient data were collected longitudinally, with median follow-up of 11.2 months (range = <0.1 to 26.9 months) from initiation of first-line therapy to study discontinuation (for death or other reason) or to data cutoff on September 30, 2019, whichever occurred first. During the follow-up period, 621 (51%) patients initiated second-line therapy, and 281 (23%) patients initiated third-line therapy (Table 1). We report HCRU for the 3 most common regimen types administered in first- through third-line; however, we note that only 18 patients received platinum-doublet chemotherapy in third-line.

PD-L1 and molecular testing

Immunohistochemical testing for PD-L1 TPS was conducted for all patients before or at initiation of first-line systemic therapy, as per the study eligibility criteria, most commonly using tissue biopsy (n = 1115 [92%]), with cytology used for 32 (3%) and a mix of other biopsy types for 58 patients (5%). For all but 4 patients, the tests were run using the pembrolizumab companion diagnostic (PD-L1 IHC 22C3 pharmDx; Agilent Technologies Japan Ltd, Hachioji, Tokyo, Japan). The distribution of PD-L1 test results, previously reported, was as follows: 529 (44%), 367 (30%), and 302 patients (25%) had tumors with PD-L1 TPS ≥50%, 1% to 49%, and <1%, respectively.[11]

Molecular testing was performed most frequently for patients with nonsquamous NSCLC (see Supplemental Table 1 in the online version at doi:10.1016/j.curtheres.2023.100712), including for *EGFR* mutations for 634 patients (89%), and for *ALK* rearrangements for 573 patients (81%) with nonsquamous NSCLC before or at initiation of first-line therapy. Just under half of nonsquamous tumors were tested for *ROS1* rearrangements (n = 331 [47%]) and a minority for *BRAF* mutations (n = 7 [1%]). The results of these molecular tests were negative, again as per study eligibility criteria.

During first-, second-, and third-line therapy, repeat PD-L1 testing was infrequent, conducted for ≤3 patients. Molecular testing was also infrequent (data not shown).

Table 1
Distribution of systemic therapy regimens by treatment line.*

Systemic therapy regimen	Patients
First-line regimen	1208 (100)
Platinum doublet	647 (53.6)
ICI monotherapy	463 (38.3)
Nonplatinum cytotoxic	98 (8.1)
Second-line regimen	621 (51.4)
ICI monotherapy	296 (47.7)
Platinum doublet	163 (26.2)
Non-platinum cytotoxic	159 (25.6)
ICI-chemotherapy combination	1 (0.2)
Tyrosine kinase inhibitor	1 (0.2)
Other	1 (0.2)
Third-line regimen	281 (23.3)
Nonplatinum cytotoxic	184 (65.5)
ICI monotherapy	75 (26.7)
Platinum doublet	18 (6.4)
Tyrosine kinase inhibitor	2 (0.7)
Other	2 (0.7)
ICI-chemotherapy combination	0

ICI = immune checkpoint inhibitor.
* Values are presented as n (%), with drug regimens shown as percentage of the relevant treatment line.

Hospitalization

The majority of patients experienced at least 1 hospitalization during each line of therapy, including 1136 (94%) during first-line, 533 (86%) during second-line, and 214 (76%) during third-line therapy (Table 2). Overall, patients had a median of 2 hospitalizations during first-line therapy (range = 0–36), 1 hospitalization during second-line therapy (range = 0–25), and 1 hospitalization during third-line therapy (range = 0–9). The overall number of hospitalizations gradually increased from 6.5 per 100 patient-weeks in first-line to 8.0 per 100 patient-weeks in third-line (Figure 1A), whereas the median length of stay in hospital increased across lines of therapy from first-line (13 days) to third-line (15 days) (Figure 1B). During first-line therapy, the numbers of hospitalizations per 100 patient-weeks were 4.8, 8.4, and 6.5 for patients receiving ICI monotherapy, platinum-doublet chemotherapy, and nonplatinum regimens, respectively (Figure 1A). The percentages of hospitalizations categorized as attributable to NSCLC treatment administration were 64%, 77%, and 73% during first-line for those receiving ICI monotherapy, platinum-doublet chemotherapy, and nonplatinum regimens, respectively, and 60%, 72%, and 69%, respectively, during second-line therapy (Table 2).

Table 2
Health care resource use: hospitalizations, outpatient visits, and radiation therapy overall among all patients and for each treatment regimen according to line of therapy when administered.*

Health care resource	All†	ICI monotherapy†	Platinum†	Nonplatinum†
≥1 Hospitalization‡				
1L	1136 (94.0)	433 (93.5)	616 (95.2)	87 (88.8)
2L	533 (85.8)	253 (85.5)	147 (90.2)	131 (82.4)
3L	214 (76.2)	55 (73.3)	13 (72.2)	142 (77.2)
No. of hospital admissions/patient§,‖				
1L	2.1 (2.1) / 2 (0–36)	2.1 (2.6) / 2 (0–36)	2.3 (1.9) / 2 (0–27)	1.6 (1.0) / 2 (0–7)
2L	1.7 (1.7) / 1 (0–25)	1.6 (1.8) / 1 (0–25)	2.0 (1.5) / 2 (0–8)	1.5 (1.4) / 1 (0–12)
3L	1.3 (1.2) / 1 (0–9)	1.4 (1.2) / 1 (0–6)	1.1 (0.9) / 1 (0–3)	1.3 (1.2) / 1 (0–9)
LOS‖, d				
1L	13 (1–266)	12 (1–266)	13 (1–163)	18 (2–166)
2L	13 (1–266)	10 (1–266)	16 (1–112)	16 (2–120)
3L	15 (1–80)	14 (2–80)	15 (3–59)	16 (1–69)
≥1 hospitalization for NSCLC treatment administration‡,¶				
1L	1020 (84.4)	373 (80.6)	571 (88.3)	76 (77.6)
2L	436 (70.2)	196 (66.2)	130 (79.8)	109 (68.6)
3L	161 (57.3)	44 (58.7)	13 (72.2)	100 (54.4)
No. of hospital admissions for NSCLC treatment administration/no. of all hospital admissions‡,#				
1L	1870/2593 (72.1)	612/951 (64.4)	1143/1484 (77.0)	115/158 (72.8)
2L	689/1051 (65.6)	290/484 (59.9)	228/318 (71.7)	170/246 (69.1)
3L	226/374 (60.4)	55/102 (53.9)	17/20 (85.0)	147/244 (60.2)
≥1 ED visit‡,**				
1L	81 (6.7)	35 (7.6)	37 (5.7)	9 (9.2)
2L	34 (5.5)	15 (5.1)	10 (6.1)	9 (5.7)
3L	15 (5.3)	4 (5.3)	0	11 (6.0)
≥1 Outpatient visit‡				
1L	1068 (88.4)	413 (89.2)	573 (88.6)	82 (83.7)
2L	559 (90.0)	265 (89.5)	146 (89.6)	145 (91.2)
3L	240 (85.4)	62 (82.7)	15 (83.3)	159 (86.4)
No. of outpatient visits				
1L	17,153	8137	8216	800
2L	6719	3250	2056	1394
3L	2395	581	168	1565
OP visit with infusion‡,††				
1L	6972 (40.7)	3875 (47.6)	2807 (34.2)	290 (36.3)
2L	2714 (40.4)	1429 (44.0)	795 (38.7)	484 (34.7)
3L	825 (34.5)	273 (47.0)	66 (39.3)	473 (30.2)
OP visit with imaging test‡,††				
1L	11,983 (69.9)	6116 (75.2)	5268 (64.1)	599 (74.9)
2L	4577 (68.1)	2282 (70.2)	1391 (67.7)	895 (64.2)
3L	1568 (65.5)	410 (70.6)	126 (75.0)	982 (62.7)
OP visit with lab test‡,††				
1L	12,126 (70.7)	5825 (71.6)	5713 (69.5)	588 (73.5)
2L	4664 (69.4)	2271 (69.9)	1398 (68.0)	984 (70.6)
3L	1582 (66.1)	411 (70.7)	105 (62.5)	1020 (65.2)
≥1 Radiation therapy‡,‡‡				
1L	242 (20.0)	82 (17.7)	155 (24.0)	5 (5.1)
2L	96 (15.5)	42 (14.2)	35 (21.5)	19 (11.9)
3L	45 (16.0)	9 (12.0)	3 (16.7)	32 (17.4)
≥1 Palliative radiation therapy for bone metastasis‡				
1L	91 (7.5)	36 (7.8)	54 (8.3)	1 (1.0)
2L	37 (6.0)	16 (5.4)	14 (8.6)	7 (4.4)
3L	13 (4.6)	3 (4.0)	0	10 (5.4)

1L= first-line therapy; 2L = second-line therapy; 3L = third-line therapy; ED = emergency department; ICI = immune checkpoint inhibitor; LOS = length of stay in hospital; NSCLC = non–small cell lung cancer; OP = outpatient.

*Patient numbers are provided in a footnote and in Table 1.

† Patient numbers in 1L, 2L, and 3L overall were 1208, 621, and 281, respectively. The numbers receiving each regimen in 1L, 2L, and 3L were as follows: ICI monotherapy, 463, 296, and 75; platinum-doublet, 647, 163, and 18; and nonplatinum regimen, 98, 159, and 184, respectively.

‡ Values are presented as n (%).

§ Values are presented as mean (SD).

‖ Values are presented as median (range).

¶ Hospital admission for NSCLC treatment administration, with no surgery or procedure conducted during the hospitalization.

Total number of hospital admissions for NSCLC treatment administration divided by total number of all-cause hospital admissions.

** ED visits were associated with a hospitalization and were also included within the hospitalization data.

†† Number of OP visits that included infusion, imaging tests, or laboratory testing and, in parentheses, their percentage of all outpatient visits during the line of therapy.

‡‡ Radiation therapy included palliative radiation therapy for bone metastasis.

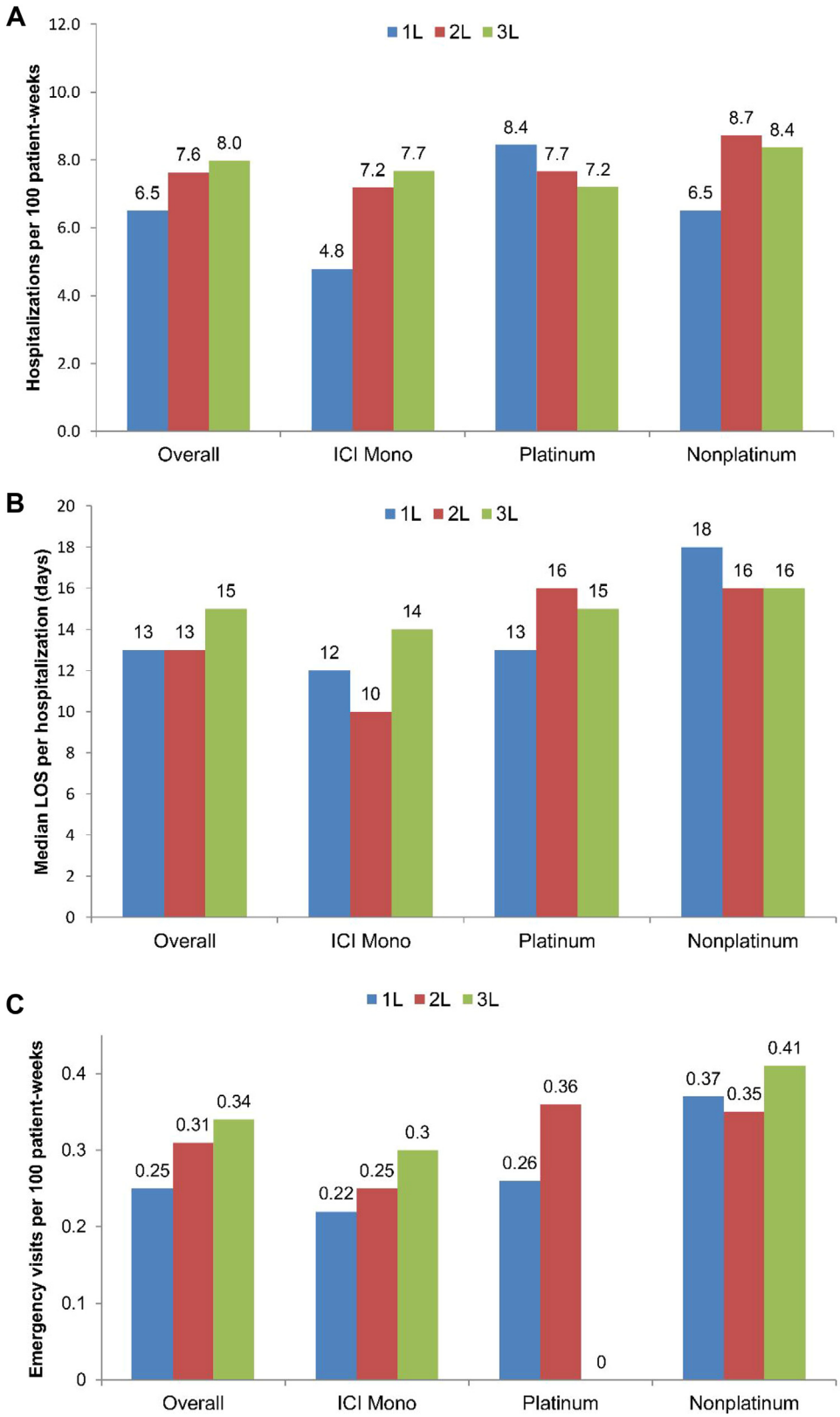

Figure 1. Hospitalizations overall among all patients and according to regimen in each line of therapy: (A) Number of hospitalizations per 100 patient-weeks. (B) Median length of hospitalization (days). (C) Number of emergency department visits associated with hospitalization per 100 patient-weeks. Patient numbers in 1L, 2L, and 3L overall were 1208, 621, and 281, respectively, and those receiving immune checkpoint inhibitor (ICI) monotherapy were 463, 296, and 75; platinum-doublet, 647, 163, and 18; and nonplatinum regimen, 98, 159, and 184 in first-line therapy (1L), second-line therapy (2L), and third-line therapy (3L), respectively. LOS = length of stay.

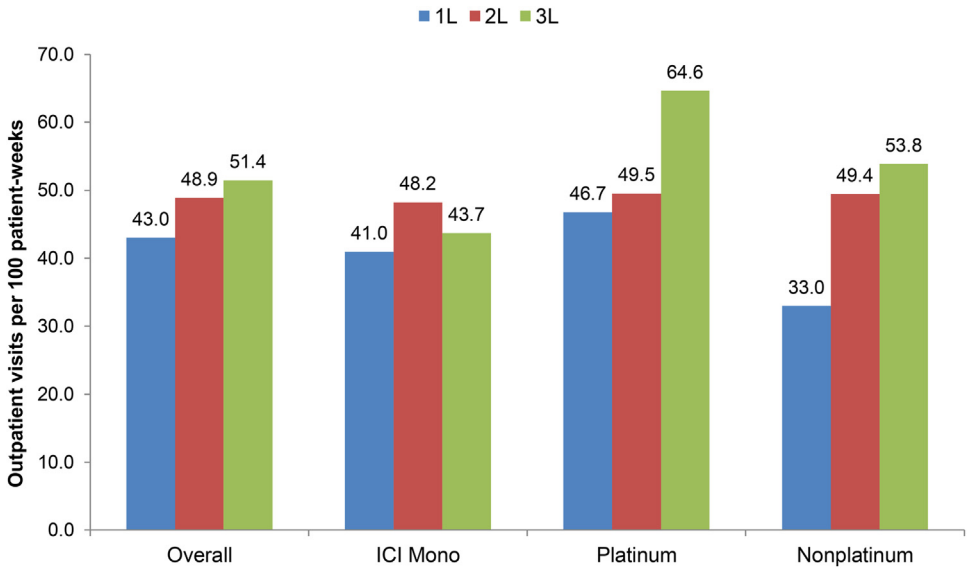

Figure 2. Number of outpatient visits per 100 patient-weeks, overall and by regimen type and line of therapy. Patient numbers in first-line therapy (1L), second-line therapy (2L), and third-line therapy (3L) overall were 1208, 621, and 281, respectively, and those receiving immune checkpoint inhibitor (ICI) monotherapy were 463, 296, and 75; platinum-doublet, 647, 163, and 18; and nonplatinum regimen, 98, 159, and 184 in 1L, 2L, and 3L, respectively.

Both ED and ICU admissions associated with hospitalization (also included within the hospitalization data) were relatively infrequent in each line of therapy. Overall, ≤7% of patients in each line of therapy were admitted to the ED as part of their hospitalization, including 81 (7%), 34 (6%), and 15 (5%) during first-, second-, and third-line therapy, respectively (Table 2). The number of ED visits was 0.25, 0.31, and 0.34 per 100 patient-weeks, respectively (Figure 1C). Only 2% of patients in each line of therapy were admitted to the ICU: overall, 27 (2%), 11 (2%), and 6 (2%) had an ICU admission during first-, second-, and third-line therapy, respectively, and the number of ICU visits was 0.07, 0.08, and 0.13 per 100 patient-weeks, respectively.

Outpatient visits

The majority of patients attended at least 1 outpatient visit during each line of therapy, including 1068 (88%) during first-line, 559 (90%) during second-line, and 240 (85%) during third-line therapy (Table 2). The number of outpatient visits per 100 patient-weeks increased with each subsequent treatment line (Figure 2). Of all outpatient visits in each treatment line, from 35% to 41% were to infusion centers, from 66% to 70% included imaging tests, and from 66% to 71% included laboratory testing. During first-line therapy, the percentages of outpatient visits for infusion therapy were 48%, 34%, and 36% for patients receiving ICI monotherapy, platinum-doublet chemotherapy, and nonplatinum regimens, respectively (Table 2). During second-line therapy, the percentages were 44%, 39%, and 35%, respectively. The number of outpatient infusion center visits per 100 patient-weeks during first-line therapy was 19.5 with ICI monotherapy, 16.0 with platinum-doublet chemotherapy, and 12.0 with nonplatinum regimens (see Supplemental Figure 1 in the online version at doi:10.1016/j.curtheres.2023.100712).

Radiation therapy

Radiation therapy was administered to 15% to 20% of all patients across each line of therapy and included palliative radiation therapy for bone metastasis for approximately 5% to 8% of patients in each line of therapy overall (Table 2). During first-line therapy, the percentage of patients administered any radiation therapy was 18% with ICI monotherapy, 24% with platinum-doublet chemotherapy, and 5% with nonplatinum regimens. The numbers of radiation therapy administered per 100 patient weeks during first-line therapy were 3.4, 12.1, and 2.1, respectively.

Imaging tests

Overall, at least 1 imaging test was conducted for 1052 patients (87%) during first-line, 556 (90%) during second-line, and 239 (85%) during third-line therapy. The number of imaging tests per 100 patient-weeks was 35.9, 39.1, and 42.1 during first-, second-, and third-line therapy, respectively, and imaging tests occurred at 70%, 68%, and 66% of outpatient visits, respectively (Table 2). In first-line therapy, 928 patients (77%) had at least 1 computed tomography scan, and 399 (33%) had at least one magnetic resonance imaging scan.

Laboratory testing

Laboratory testing was conducted for 1051 patients (87%) during first-line, 552 (89%) during second-line, and 241 (86%) during third-line therapy, and the number of laboratory tests per 100 patient-weeks was 106.2, 115.4, and 120.5 during first-, second-, and third-line therapy, respectively. Similar to imaging tests, laboratory testing was frequently conducted during outpatient visits, including at 71%, 69%, and 66% of outpatient visits during first-, second-, and third-line therapy, respectively (Table 2). The mean (SD) number of tests per laboratory visit was 3.3 (1.7), 3.2 (1.7), and 3.1 (1.7), respectively.

Discussion

This large, retrospective observational study describes HCRU in Japan during first- through third-line treatment of 1208 patients with advanced/metastatic NSCLC with no known genomic alterations during the period from July 2017 through September 2019. Testing for tumor PD-L1 expression before or at initiation of first-line therapy was required for study inclusion, and administered first-line therapies were largely aligned with contemporaneous

Japan Lung Cancer Society guidelines, as previously described.[11,14] We observed that patterns of HCRU differed, particularly during first-line therapy, among the 3 common systemic anticancer therapy regimens. For example, during first-line therapy, the numbers of hospitalizations per 100 patient-weeks were 4.8, 8.4, and 6.5 for patients receiving ICI monotherapy, platinum-doublet chemotherapy, and nonplatinum regimens, respectively, whereas the percentages of outpatient visits for infusion therapy were 48%, 34%, and 36%, respectively. These patterns could be explained by an uneven distribution of prognostic factors at baseline (namely, patient or clinical characteristics associated with treatment). An alternative explanation could be a decreased reliance on hospitalization for ICI monotherapy administration relative to other treatments, a supposition supported by the fact that patients treated with first-line ICI monotherapy had a lower percentage of hospital admissions categorized as attributable to NSCLC treatment administration (64%) relative to the other 2 regimens (77% and 73%, respectively), with the same pattern observed during second-line therapy. Finally, different patterns of HCRU by regimen type during follow-up could potentially be explained by differences in clinical outcomes among the treatment types.

A shift from inpatient to outpatient therapy from 2008 to 2018 was reported also in a single-center study of medical costs for patients with advanced lung cancer that included 330 patients with NSCLC.[12] The authors speculated that this shift was occurring because of newer anticancer agents such as ICIs and tyrosine kinase inhibitors, for which administration can be managed on an outpatient basis, and our findings support this speculation. Although patients in Japan may receive infusions in either inpatient or outpatient settings, infusions have historically been administered more often in the hospital setting to manage the administration of hydration and antiemetic and allergy medications before treatment with chemotherapy. Indeed, the overall frequency of infusion center visits was much greater in the present study than in the preimmunotherapy era, when these visits comprised only 3% of all outpatient visits during first-line therapy in 1 study.[15]

Prior studies of hospitalizations and outpatient visits for advanced NSCLC in Japan are few and mostly differed from our study in patient population and end points.[7,9,15] We found that the majority of patients (76% to 94%), overall, were hospitalized at least once during each line of therapy, and the number of hospital admissions per 100 patient-weeks increased as patients advanced from first- to third-line therapy, as did the numbers per 100 patient-weeks of ED visits and ICU visits associated with hospitalization, although these occurred infrequently. An earlier study that included 175 Japanese patients treated for advanced NSCLC from 2011 to mid-2015, thus preimmunotherapy, found that 81% and 84% of patients were hospitalized at least once during first- and second-line therapy, respectively, and the numbers of hospitalizations per 100-patient-weeks were 5.5 and 5.1 in first- and second-line, respectively, fewer than in the present study (6.5 and 7.6 per 100 patient-weeks, respectively), whereas median hospital stays were 15 and 17 days, respectively, slightly longer than the median of 13 days in both first- and second-line in the present study.[9,15] In a more recent study evaluating HCRU costs during the first year after a cancer diagnosis in 2017, the approximately 35,000 patients with stages III and IV lung cancer (all types) experienced annual medians of 3 and 2 hospitalizations with stage III and IV diagnoses, respectively, and medians of 46 and 37 hospital days per year, respectively.[7]

With regard to outpatient visits, the number was 38 per 100 patient-weeks during both first- and second-line therapy in the earlier preimmunotherapy study,[15] whereas we found that the number of outpatient visits was somewhat greater at 43 and 49 per 100 patient-weeks during first- and second-line therapy, respectively. These findings could reflect shorter hospital stays providing more opportunity for outpatient visits to occur, a transition from inpatient to outpatient visits for drug administration, differences in clinical outcomes for patients with advanced NSCLC over time, or methodological differences in the present study relative to the earlier one. Watanabe et al[7] reported annual medians of 19 and 11 outpatient visits for stages III and IV lung cancer, respectively. The 2017 study and 2 others examining the costs of treating advanced NSCLC in Japan did not provide similar end points to contrast with those in our study[7,12,16]; and we were unable to identify another detailed evaluation of HCRU for advanced NSCLC in Japan since 2017.

We observed that molecular testing of nonsquamous tumors for *EGFR/ALK* gene alterations before or at initiation of first-line therapy was common in this study, whereas other baseline molecular testing was less common, a trend that had not changed much since the preimmunotherapy era (2011–2015),[17] despite the introduction of new biomarker tests since then. Namely, *ROS1* rearrangement tests were reimbursed starting in June 2017 and *BRAF* mutation tests were covered by a patient access program starting in April 2018. After the start of first-line therapy, PD-L1 and molecular testing were infrequent.

This large retrospective study was conducted at multiple centers geographically distributed throughout Japan in line with the distribution of the Japanese population, as previously described.[11] In addition, chart abstraction was conducted by trained abstractors, and there were no relevant changes in study procedures because of the COVID-19 pandemic,[11] which also had no influence on patient outcomes, as follow-up ended (on September 30, 2019) before the first case of COVID-19 was identified in Japan (January 16, 2020).

Our study has several limitations that should be mentioned. The study was descriptive in nature and thus was not designed to make comparisons by treatment regimen. It was also not designed to identify causal factors that explain HCRU variation. Moreover, the follow-up period was shorter for patient populations in second- and third-line than for the full patient population receiving first-line therapy, and this fact could affect measures for which administrative censoring occurred. Therefore, caution should be used when interpreting HCRU in those later lines of therapy. We did not consider treatment sequence, and therefore the extent to which first-line therapy may have influenced HCRU in later lines has not been examined. Finally, our study did not evaluate HCRU changes over time within a given line of therapy. For example, future studies could apply longitudinal methods to better understand HCRU variation at specific time periods within the first-line setting.

We did observe that first-line hospitalization patterns for NSCLC treatment administration varied by treatment type, with potentially less hospital-based NSCLC treatment administration observed among patients receiving ICI monotherapy relative to other treatment types. This pattern, including by age subgroup, warrants further study in Japan, where the hospitalization burden is high. In addition to the HCRU perspective, future studies should also consider the humanistic implications of differences in hospitalization patterns by treatment type. For example, fewer hospitalizations and fewer days in the hospital during the treatment journey could be associated with reduced burden on patients, caregivers, and hospital resources, in addition to a reduced economic burden on the Japanese health insurance body and government.

Conclusions

The results of this study provide information about the primary components of care for NSCLC accounting for HCRU by line of therapy and treatment regimen for patients in Japan with advanced NSCLC and no actionable genomic aberration treated in 2017 to

2019. Our findings, although solely descriptive, showed differing patterns of HCRU during first-line therapy among the 3 common systemic anticancer therapy regimens for advanced NSCLC in Japan and suggest that further research is needed to investigate these apparent differences by treatment regimen.

Declaration of Competing Interest

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M. L. Santorelli, K. Taniguchi, T. Kamitani, M. Abe, and T. Burke conceptualized and designed the study. Y. Goto, K. Kawamura, T. Fukuhara, Y. Namba, K. Aoe, T. Shukuya, T. Tsuda, and H. Nokihara participated in data collection and investigation. All authors were involved in review and interpretation of the data. M. L. Santorelli, K. Taniguchi, T. Kamitani, and T. Burke contributed to drafting the manuscript. All authors critically reviewed and approved the manuscript for submission.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2023.100712.

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