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Toxicity of initial chemotherapy in older patients with lung cancers

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Abstract

Objectives—Despite the growing number of elderly patients with lung cancers, we lack adequate information about how best to treat them. A phase III trial demonstrated a survival benefit of doublet chemotherapy in elderly patients with lung cancers compared to single agents at the cost of increased toxicity. We undertook this study to identify and describe chemotherapy-associated toxicity patterns among elderly patients treated for lung cancers.

Materials and methods—We reviewed records of patients age 70 or older with metastatic lung cancers who received initial chemotherapy at the Memorial Sloan-Kettering Cancer Center during 2008 and 2009.

Results—We identified 70 patients: 28 (40%) completed at least 4 cycles of chemotherapy without dose reduction but 31 (44%) required hospitalization for toxicity. Baseline albumin <3.5 g/dL and anemia were associated with grade 3–5 chemotherapy-associated toxicity. Also, an increase in platelets from cycle 1 to cycle 2 was associated with chemotherapy-associated toxicity. No other statistically significant associations between chemotherapy-associated toxicity and putative biologic and functional risk factors, including age and performance status, were identified.

Conclusion—Patients deemed eligible for chemotherapy by their physicians were just as likely to have severe chemotherapy-associated toxicity requiring hospitalization as to finish an initial course of therapy without any serious problems. An increase in platelet count from cycle 1 to

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cycle 2 was associated with increased toxicity. Additional research, such as exploration of inflammatory cytokines (PDGF, IL6, and IGF-1) to identify the mechanisms of chemotherapy tolerance and prospective evaluation and validation of existing metrics, is needed so that all patients can be appropriately risk stratified.

Keywords

Elderly; Chemotherapy toxicity; Lung cancers; Geriatric assessment

1.Introduction

More than two-thirds of patients with lung cancers in the United States are over 65 years of age. The median age at the time of diagnosis is now 70 years.[1,2] The majority of patients present with advanced disease where chemotherapy is the mainstay of treatment. Initial platinum-based regimens have become the standard of care based on trials showing their survival benefit in young and old alike.[3–7]

Despite the increasing prevalence of lung cancers among elderly individuals, little prospective data exist regarding their treatment.[8–10] Most data regarding older patients are extrapolated from trials enrolling predominantly younger individuals, or obtained from subgroup analyses.[11–15] A Cancer and Leukemia Group B (CALGB) randomized trial comparing carboplatin and paclitaxel to paclitaxel alone did stratify patients at the time of randomization based on age (<70 versus ≥70). Among the older patients, as well as the entire cohort, combination chemotherapy improved the response rate and time to progression but not overall survival.[16] Similar to other studies, persons over 70 comprised only 27% of the overall study group. The results of a phase III trial comparing paclitaxel and carboplatin to single-agent therapy with either gemcitabine or vinorelbine in patients age 70–89 with Eastern Cooperative Oncology Group performance status 0–2 demonstrated a four-month benefit in median survival in those who received the carboplatin-based doublet treatment (10 versus 6 months, p=0.00004) but increased grade 3 and 4 hematologic toxicity: neutropenia (54% versus 14%, p<0.00001); febrile neutropenia (10% versus 3%, p=0.004); and thrombocytopenia (6% versus 1%, p=0.004).[17]

Like their younger counterparts, many elderly patients derive benefit from platinum-based doublet chemotherapy. However, compared to younger individuals, less of the elderly are able to tolerate this treatment regimen. Therefore, prognostic functional and biologic risk factors must be identified to help risk stratify elderly patients and inform appropriate treatment interventions. Several instruments are in development to prospectively evaluate elderly patients and identify those at high risk for severe chemotherapy-associated toxicity.[18–29] None of these instruments, however, has yet been refined for tumor type, disease stage, or treatment regimen. We undertook this retrospective review of elderly individuals with metastatic lung cancers treated over a two-year time period at Memorial Sloan-Kettering Cancer Center's (MSKCC) Manhattan outpatient facility in order to help identify and describe chemotherapy-associated toxicity patterns in these patients. Additionally, we examined the association between chemotherapy-associated toxicity and several putative functional and biologic risk factors for toxicity.

2. Materials and methods

After obtaining IRB approval, a search of the MSKCC electronic medical records identified all patients with previously untreated stage IV non-small cell lung cancers (NSCLC) who underwent initial consultation with a thoracic medical oncologist between January 1, 2008 and December 31, 2009 and were ≥70 years of age at the time of consultation. In order to have appropriate follow-up data, we included only patients who received treatment at the

MSKCC Manhattan site. The following data were captured from chart reviews: age; sex; tumor stage; presence of brain metastases; tumor histology; presence of EGFR and KRAS mutations; comorbid medical conditions to calculate Charlson comorbidity index[30]; concurrent medications; Karnofsky Performance Status (KPS); activities of daily living (ADLS) and instrumental activities of daily living (IADLS) dependence; social support; fall history; weight loss; smoking history; baseline hemoglobin; baseline creatinine clearance; baseline liver function levels; cognitive impairment; treatment regimen including doses and schedule; chemotherapy complications including grade 3–5 hematologic and non-hematologic toxicity; treatment delay; dose reduction; hospitalization; and discontinuation of therapy due to toxicity. Notably, at our institution, all patients complete an ambulatory nursing adult health screen questionnaire prior to their initial consultation with a medical oncologist. As part of this questionnaire, patients are specifically asked whether they have fallen in the past year. Additionally, several questions pertain to the need for assistance with ADLS and IADLS as well as the availability of social support.

The relationship between age (less than 75 versus 75 or older), sex, KPS (80% and higher versus 70% and lower), histology (adenocarcinoma versus squamous), Charlson comorbidity index (0–1 versus 2 or greater), brain metastases, unintentional weight loss, fall history, albumin (less than 3.5 g/dL versus 3.5 g/dL or higher), anemia, ADL dependence, IADL dependence, platinum chemotherapy and each measure of toxicity (grade 3–5 hematologic toxicity, grade 3–5 non-hematologic toxicity, hospitalization, dose reduction, and treatment delay) was assessed using Fisher's exact tests. The relationship between change in blood counts from the beginning of cycle 1 to the beginning of cycle 2 and a composite toxicity outcome including grade 3–5 chemotherapy-associated toxicity was assessed using Wilcoxon tests. A waiver of authorization was granted by the MSKCC Institutional Review Board for this project.

3. Results

Between January 1, 2008 and December 31, 2009, a total of 984 patients age 70 or older were seen by a thoracic medical oncologist at the MSKCC Manhattan outpatient facility. Only 70 of these patients met the inclusion criteria defined above for this analysis and their demographics are outlined in Table 1. The majority of those who were ineligible did not receive follow-up care at MSKCC Manhattan or did not have metastatic disease: 38% did not receive follow-up care at MSKCC Manhattan; 15% did not have NSCLC; 23% did not have stage 4 disease; 13% had prior therapy; 6% received therapy with a tyrosine kinase inhibitor; 2% enrolled in clinical trials; and 3% did not receive chemotherapy either due to patient preference or physician assessment as too unfit for therapy.

The median age of patients included in this study was 75 (range 70–92). The majority were men who formerly smoked. The prevalence of comorbid medical conditions was assessed using the Charlson comorbidity index, which assigns relative point values for a variety of medical diseases and conditions that are associated with increased risk of death at 1 year.[30] The median albumin at the time of initial consultation was 3.6 g/dL (range 2.1–4.7 g/dL) with 39% of this cohort having an albumin <3.5 g/dL. The median KPS in this cohort was 80% (range 60–90%). Complete ambulatory health screening questionnaires were available for 83% (58 patients (pts)) of this cohort. From the information available on these forms and from physician notes, dependence in ADLS was noted in 4 patients (6%) and dependence in IADLS was noted in 6 patients (9%). Of the 40% of patients (28 pts) with tumors tested for EGFR and KRAS mutations, 11% (3 pts) of tumors were found to have an EGFR mutation and 29% (8 pts) a KRAS mutation.

Eighty percent (56 pts) of patients received doublet therapy and 64% (45 pts) received platinum doublet therapy. There was wide variation in the particular chemotherapy regimen used, which appeared to be influenced by tumor histology. Eleven different regimens were used for the 49 patients with adenocarcinomas, with the most commonly used being carboplatin and pemetrexed (22 patients, 45%) and pemetrexed alone (9 patients, 19%). Nine different regimens were used for the 21 patients with other histologies, with 6 patients (29%) receiving carboplatin and gemcitabine and 4 patients (19%) receiving carboplatin and pemetrexed. A small group of patients (11 pts (16%)) received upfront dose reductions.

Treatment toxicity is summarized in Table 2. Only 40% (28 pts) of patients completed 4 cycles of chemotherapy without dose reduction (Fig. 1A). Another 20% (14 pts) were able to complete 4 cycles with dose reduction, but the remaining 40% (28 pts) were unable to complete 4 cycles. Thirty-one patients (44%) required hospitalization (Fig. 1B) and 39 patients (56%) experienced at least one grade 3–5 toxicity. The most common hematologic toxicities were grade 3 anemia, grade 3 neutropenia, and grade 3 leukopenia; the most common non-hematologic toxicities were thromboembolic events, dyspnea, infection, and fatigue. Only 2 patients (3%) experienced neutropenic fever and 3 patients (4%) experienced grade 3 or 4 thrombocytopenia. Thirteen patients (19%) died within 60 days of receiving a dose of chemotherapy: 12 patients due to disease progression and 1 patient due to treatment-related toxicity.

Neither age nor performance status was associated with any toxicity (Table 3). Baseline albumin <3.5 g/dL and anemia had statistically significant associations ($p=0.02$ and $p=0.04$, respectively) with grade 3–5 hematologic toxicity. KPS ≤70% and unintended weight loss were associated with dose reduction or discontinuation for toxicity ($p=0.02$ and $p=0.05$, respectively). Administration of doublet chemotherapy had a statistically significant association with hospitalization ($p=0.02$) and was also associated with a trend toward improved survival (11 months versus 7 months, $p=0.06$). However, given that patients were highly selected by their physicians for this therapy, it is impossible to determine if this trend toward improved outcome is the effect of chemotherapy.

As displayed in Table 3, no other baseline characteristics or treatment variables had a significant association with toxicity, dose reduction, or discontinuation due to toxicity. In a multivariate analysis, anemia and albumin <3.5 g/dL remained independently associated with grade 3–5 hematologic toxicity while KPS and weight loss were not significantly associated with dose reduction or discontinuation for toxicity. Given the small number of the patients with upfront dose reductions, we are unable to identify any statistically significant association between upfront dose reductions and the presence or absence of chemotherapy-associated toxicity or hospitalization. Among patients who experienced grade 3–5 chemotherapy-associated toxicity, there was a statistically significant increase in platelet counts from the beginning of cycle 1 to the beginning of cycle 2: 36% increase among those with composite toxicity versus 2% increase among those without composite toxicity ($p=0.005$). No other change in blood count was associated with chemotherapy-associated toxicity.

4. Discussion

The goal of this study was to examine a single institution's experience with giving initial chemotherapy to elderly patients with metastatic NSCLC in order to describe patterns of chemotherapy-associated toxicity. Many in this cohort experienced significant toxicity and a large proportion (44%) required hospitalization, possibly reflecting the true toxicity of these agents in clinical practice without the application of rigorous clinical trial entry requirements. However, an equal number of patients (40%) tolerated at least 4 cycles of

chemotherapy without dose reduction. The rate of hospitalization among these patients was high and likely reflects the absence of application of rigorous clinical trial entry requirements. Performance status and comorbid disease burden are often used to gauge a patient's ability to tolerate chemotherapy; however, these risk factors are clearly insufficient to predict toxicities once the decision to begin chemotherapy has been made.

In fact, none of the 13 baseline demographic or treatment variables that we examined were reliably associated with toxicity. Rather, only pre-existing hypoalbuminemia and anemia were associated with grade 3–5 hematologic toxicity, which likely reflects decreased bone marrow reserve and poor nutritional status, and thus their association with hematologic toxicity is not unexpected. However, not all of these baseline demographic or treatment variables were retrospectively captured with the same accuracy. That is, while some variables were explicitly captured prior to initiating therapy, such as KPS, fall history, and weight loss, other metrics were inadequately queried, such as ADLS, IADLS, and social support. This likely contributed to the low incidence of dependence in ADLS and IADLS which would bias these results. Clearly, prospective study fully capturing data regarding the putative biologic and functional risk factors for chemotherapy-associated toxicity as well as efforts to validate existing assessment tools in this patient population is needed.

Among this cohort, however, for those who experienced grade 3–5 chemotherapy-associated toxicity, there was a statistically significant increase in platelet counts from the beginning of cycle 1 to the beginning of cycle 2. The significance of this observation is unclear. Chemotherapy-associated toxicity was not associated with any other change in blood count. There are several growth factors and cytokines that can increase platelet counts as a secondary activity, and some inflammatory markers, such as IL6 and IGF-1, have been associated with lung cancers. Therefore, an increase in platelet count despite treatment with chemotherapy may simply reflect persistent lung cancer.

As eluded to above, the current analysis has several limitations including: 1) the retrospective nature of the study, which limits our ability to reliably capture information about well-known risk factors such as ADL and IADL dependency; 2) the use of only a single, outpatient, tertiary-care institution, as these patients may not be reflective of all elderly patients with lung cancers; and 3) the limited size of this convenience sample, which leaves this analysis underpowered. Furthermore, our now standard assessment using the Timed Get Up and Go test was not in place during the study period.

Despite these limitations, it is clear that current physician assessment practices are inadequate; patients selected for chemotherapy are as likely to be hospitalized from chemotherapy-associated toxicity as they are to tolerate treatment without serious complications. However, given the limitations of this retrospective study, our other observations are merely hypothesis generating and underscore the need for additional prospective research to identify the biologic mechanisms of chemotherapy tolerance. Disease-, stage-, and treatment-specific markers predictive of tolerance will likely be necessary. Using the Timed Get Up and Go test is one strategy for toxicity risk assessment we plan to pursue. Additionally, further prospective investigation of potential early markers of treatment tolerance such as platelet count and inflammatory cytokines is warranted to better understand our observation. Ultimately, prognostic assessment tools will be used in the routine pretreatment assessment of all patients for risk stratification so that upfront treatment modifications and interventions can be made to prevent and/or ameliorate toxicity while simultaneously facilitate receipt of life-prolonging therapies by those at low risk for complications.

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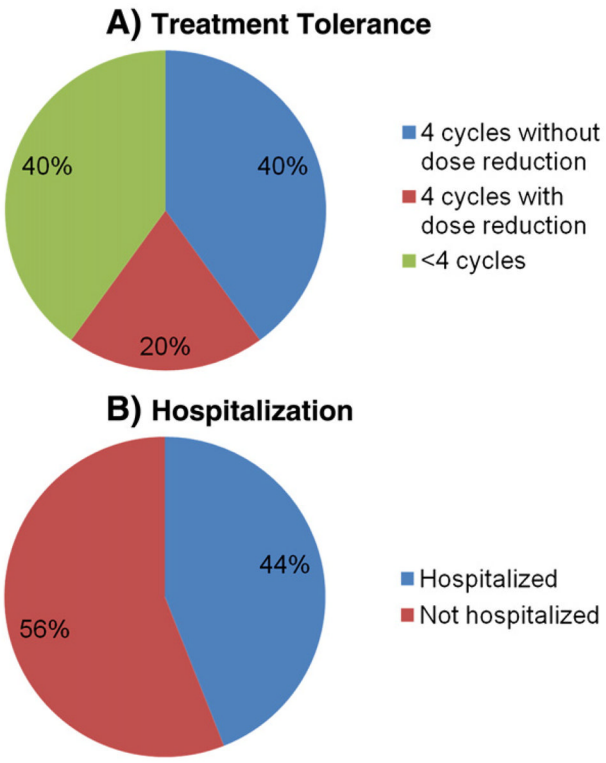

Fig 1.

Treatment tolerance and hospitalization. A) Depicted above are the percentages of patients who were and were not able to tolerate 4 cycles of chemotherapy without dose reduction. B) Depicted above is the percentage of patients who did and did not require hospitalization during their initial 4 cycles of chemotherapy.

Table 1

Patient characteristics.

Demographic	N (%)
Age (years)	
70–74	32 (46)
75–79	22 (31)
80–84	9 (13)
≥85	7 (10)
Sex	
Male	50 (71)
Female	20 (29)
KPS (%)	
80–100	45 (64)
≤70	25 (36)
Smoking	
Current	8 (11)
Former	57 (82)
Never	5 (7)
Mutation testing	28 (40)
EGFR	3 (11)
KRAS	8 (29)
Histology	
Adenocarcinoma	49 (70)
Squamous	11 (16)
Other[1]	10 (14)
Charlson comorbidity index	
0	28 (40)
1–2	30 (43)
3–4	11 (16)
≥5	1 (1)
Brain metastases	
Yes	19 (27)
No	51 (73)
Weight loss	
Yes	26 (37)
No	44 (63)
Fall history	
Yes	10 (14)
No	60 (86)

KPS=Karnofsky Performance Status;

[1] 9 cases were poorly differentiated carcinoma, 1 case was large cell carcinoma.

Table 2

Common toxicities.

Toxicity [1]	Number (%)
Hospitalization	31 (44%)
Any grade 3–5 toxicity	39 (56%)
Grade 3–5 hematologic toxicity	22 (31%)
Grade 3–5 non-hematologic toxicity	27 (39%)
Most common hematologic toxicities	
Grade 3 neutropenia	7 (10%)
Grade 3 anemia	14 (20%)
Grade 3 leukopenia	4 (6%)
Most common non-hematologic toxicities	
Grade 3 or 4 thromboembolic event	9 (13%)
Grade 3 dyspnea	7 (10%)
Grade 3 infection	7 (10%)
Grade 3 fatigue	5 (7%)

Listed above are the most common hematologic and non-hematologic toxicities. Toxicities noted in <6% of patients included: grade 4 leukopenia, grade 4 neutropenia, grade 4 anemia, grade 4 thrombocytopenia, grade 3 thrombocytopenia, grade 3 fall, grade 3 weakness, grade 3 diarrhea, grade 3 hypercalcemia, grade 3 amylase elevation, grade 3 lipase elevation, grade 3 rash, grade 3 pain, grade 3 hypertension, grade 3 digitalis toxicity, grade 3 acute kidney injury, grade 3 atrial fibrillation, and grade 3 mental status changes.

[1]The toxicities noted above are not mutually exclusive. A single patient could have experienced more than one specific toxicity. The hospitalizations noted above are for chemotherapy-associated toxicity.

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Table 3

Toxicity associations.

Variable	Incidence	Grade 3/4 hematologic toxicity (%)	p-value	Grade 3/4 non-hematologic toxicity (%)	p-value	Hospitalization	p-value	Dose reduction or discontinuation for toxicity	p-value	Treatment delay	p-value
Age											
70–74	32	10 (31)	1.0	11 (34)	0.62	15 (47)	0.63	17 (53)	0.63	12 (38)	0.62
≥75	38	12 (32)		16 (42)		15 (39)		23 (61)		12 (32)	
Sex											
Male	50	15 (30)	0.78	19 (38)	1.0	22 (44)	0.80	30 (60)	0.59	17 (34)	1.0
Female	20	7 (35)		8 (40)		8 (40)		10 (50)		7 (35)	
KPS											
80–100	45	13 (29)	0.60	18 (40)	0.80	18 (40)	0.62	21 (47)	0.02	16 (36)	0.80
≤70	25	9 (36)		9 (36)		12 (48)		19 (76)		8 (32)	
Histology[1]											
Adenocarcinoma	49	15 (31)	0.73	19 (39)	0.50	21 (43)	0.52	28 (57)	1.0	17 (35)	1.0
Squamous	11	4 (36)		6 (55)		6 (55)		6 (55)		4 (36)	
Charlson comorbidity index											
0–1	44	12 (27)	0.43	15 (34)	0.45	19 (43)	1.0	25 (57)	1.0	16 (36)	0.80
≥2	26	10 (38)		12 (46)		11 (42)		15 (58)		8 (31)	
Brain metastases											
Yes	19	5 (26)	0.77	9 (47)	0.41	8 (42)	1.0	14 (74)	0.11	7 (37)	0.78
No	51	17 (33)		18 (35)		22 (43)		26 (51)		17 (33)	
Unintended weight loss											
Yes	26	9 (35)	0.79	7 (27)	0.14	10 (38)	0.62	19 (73)	0.05	9 (35)	1.0
No	44	13 (30)		20 (45)		20 (45)		21 (48)		15 (34)	
Fall history											
Yes	10	4 (40)	0.71	3 (30)	0.73	2 (20)	0.17	6 (60)	1.0	2 (20)	0.48
No	60	18 (30)		24 (40)		28 (47)		34 (57)		22 (37)	
Albumin											
<3.5 g/dL	27	4 (15)	0.02	11 (41)	0.81	11 (41)	0.81	18 (67)	0.22	7 (26)	0.31
≥3.5 g/dL	43	18 (42)		16 (37)		19 (44)		22 (51)		17 (40)	

Variable	Incidence	Grade 3/4 hematologic toxicity (%)	p-value	Grade 3/4 non-hematologic toxicity (%)	p-value	Hospitalization	p-value	Dose reduction or discontinuation for toxicity	p-value	Treatment delay	p-value
Anemia											
Yes	31	14 (45)	0.04	14 (45)	0.33	13 (42)	1.0	20 (65)	0.33	10 (32)	0.80
No	39	8 (21)		13 (33)		17 (44)		20 (51)		14 (36)	
ADLs											
Dependent	4	3 (75)	0.09	1 (25)	1.0	1 (25)	0.63	4 (100)	0.13	1 (25)	1.0
Independent	66	19 (29)		26 (39)		29 (44)		36 (55)		23 (35)	
IADLs											
Dependent	6	3 (50)	0.37	1 (17)	0.39	1 (17)	0.23	5 (83)	0.23	1 (17)	0.66
Independent	64	19 (30)		26 (41)		29 (45)		35 (55)		23 (36)	
Chemotherapy											
Platinum	45	16 (36)	0.42	18 (40)	0.80	22 (49)	0.21	22 (49)	0.08	17 (38)	0.44
No platinum	25	6 (24)		9 (36)		8 (32)		18 (72)		7 (28)	
Doublet chemo											
Yes	56	20 (36)	0.20	24 (43)	0.22	28 (50)	0.02	29 (52)	0.08	20 (36)	0.76
No	14	2 (14)		3 (21)		2 (14)		11 (79)		4 (29)	

[1]10 cases that were neither adenocarcinoma nor squamous were excluded from this analysis; the majority of these were poorly differentiated non-small cell carcinoma.