Trends in Neutropenia-Related Hospitalization in Older Patients With Non-Hodgkin Lymphoma Receiving Myelosuppressive Chemotherapy in the United States: 1995–2015

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Introduction

- Febrile neutropenia (FN) is a serious complication among patients receiving myelosuppressive chemotherapy and is associated with substantial morbidity, mortality, and healthcare costs[1,2]
- Clinical trials have shown the efficacy of primary prophylaxis with colony-stimulating factor (PP-CSF) in reducing FN risk,[3,4] but few population-based studies have examined trends in PP-CSF use and FN incidence in older patients over the past 20 years
- Here we describe trends in regimens of myelosuppressive chemotherapy by FN risk category, PP-CSF use, and risk of neutropenia-related hospitalization focusing on elderly patients with non-Hodgkin lymphoma (NHL) initiating myelosuppressive chemotherapy

Methods

- **Data source:** Medicare 5% (1994–2007) and 20% (2007–2015) sample data
- **Inclusion criteria:**
  - Initiated myelosuppressive chemotherapy for NHL treatment each year from 1995 to 2015, aged ≥ 66 years at initiation of myelosuppressive chemotherapy, and survived ≥ 6 days after initiation
  - Continuously enrolled in Medicare Parts A and B for at least 12 months before myelosuppressive chemotherapy initiation (first myelosuppressive chemotherapy treatment in the year with no claims for myelosuppressive chemotherapy agents in the preceding 12 months)
- **Exclusion criteria:**
  - Received radiotherapy or had evidence of stem cell transplantation in the 12 months before and 6 days after initiation of myelosuppressive chemotherapy
- **Chemotherapy cycle:**
  - The first myelosuppressive chemotherapy cycle started on the initiation date (day 1) and ended at the next administration at least 6 days, but no more than 35 days, after initiation
  - If no second myelosuppressive chemotherapy cycle started before day 35, the first cycle was considered completed at the earliest of day 35 after initiation, the day before regimen change, death, disenrollment from Part A or B, or September 30, 2015
- **Chemotherapy regimen:**
  - Defined based on myelosuppressive chemotherapy agents on Part A outpatient (OP)/Part B (PB) claims from day 1 to day 6 of the first cycle and, on the same claims, an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for NHL (200.xx, 202.xx)
  - National Comprehensive Cancer Network® (NCCN®) guidelines[5] recommend use of myeloid growth factors for patients receiving chemotherapy regimens with high (> 20%) or intermediate (10%–20%) risk for FN with at least one patient risk factor (eg, age ≥ 65 years)
  - Regimens were classified into high or intermediate FN risk category based on the most recent classification in the NCCN® guidelines 2005–2017.[5] Regimens not classified as high or intermediate FN risk anytime during the study period were grouped into an "Other" FN risk category
- **PP-CSF:** defined as an administration of pegfilgrastim or any short-acting CSF (filgrastim, tbo-filgrastim, filgrastim-sndz, or sargramostim) in OP/PB claims at or up to 5 days after completion of the first cycle of chemotherapy
- **Neutropenia-related hospitalization:** identified from inpatient claims with the ICD-9-CM diagnosis code 288.0X in the first five positions between day 7 and the last day of the first cycle
- **Statistical analysis:**
  - We describe trends in proportions of patients receiving myelosuppressive chemotherapy regimens by FN risk category, with PP-CSF use, and with neutropenia-related hospitalization in the first cycle
  - Trends in neutropenia-related hospitalization rates were further evaluated using a logistic regression model with calendar year treated as a continuous variable and functional form estimated by a penalized spline after adjusting for baseline patient characteristics

Results

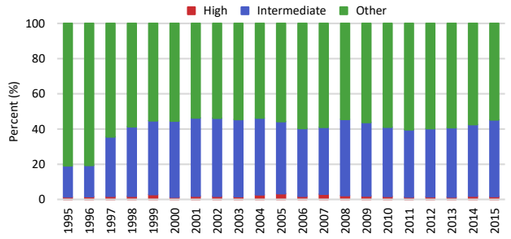
- Yearly cohorts included 538–717 eligible patients from 1995 to 2007 and 1877–2640 patients from 2008 to 2015. The proportion of patients aged ≥ 80 years increased from 39% in 1995 to 44% in 2015 **(Table 1)**
- Patients who received high/intermediate FN risk regimens accounted for < 20% before 1997, 36% in 1997, and 40%–46% between 1998 and 2015 **(Figure 1)**; of these, CHOP-21 (cyclophosphamide, doxorubicin, and vincristine every 21 days +/- rituximab) was used most often (88%–96%)
- Overall, PP-CSF use increased from 8% in 1995 to almost 60% in 2015, mainly due to the introduction of pegfilgrastim in 2002 **(Figure 2)**
- PP-CSF use was more common in patients receiving high/intermediate FN risk regimens than in patients receiving other regimens **(Figure 3)**
- Overall, unadjusted incidence of neutropenia-related hospitalization decreased from 7% in 1995 to 4% in 2015 **(Figure 4)**
- Change point in trend was detected at 2010 (we cannot confirm 1999 as a change point, probably due to small sample sizes); incidence of neutropenia-related hospitalization decreased, on average, 6% each year before 2010 ($P < 0.0001$) and was flat from 2010 onward ($P = 0.6$) after adjustment for changed patient characteristics

Table 1. Patient characteristics for selected years from 1995 to 2015

Characteristic	Medicare 5% sample			Medicare 20% sample		
	1995 N = 538	2001 N = 610	2007 N = 695	2008 N = 2620	2014 N = 2372	2015 N = 1877
Age category, %						
66–69 years	13.2	14.3	15.7	13.4	14.8	13.2
70–74 years	25.8	24.4	22.0	19.2	21.9	21.6
75–79 years	22.1	22.3	18.6	21.0	19.4	21.5
80+ years	38.8	39.0	43.7	46.3	43.9	43.8
Race, %						
White	95.2	93.1	94.0	93.2	92.2	92.6
Black	2.4	3.1	2.2	3.3	3.5	3.0
Other	2.4	3.8	3.9	3.5	4.3	4.4
Number of comorbidities, %						
0	44.8	33.3	30.5	26.4	26.5	23.9
1	29.9	28.9	24.9	29.0	24.3	27.1
2	12.8	20.0	21.3	21.8	19.5	20.0
≥ 3	12.5	17.9	23.3	22.8	29.7	29.0
Length of hospital stay at baseline, %						
< 1 day	48.1	47.4	51.8	50.1	56.7	56.1
1–5 days	15.4	21.0	19.1	20.9	18.2	18.9
≥ 6 days	36.4	31.6	29.1	29.0	25.1	25.0
Neutropenia-related hospitalization at baseline, %	5.0	3.4	2.4	3.1	3.2	3.8
High/Intermediate FN risk regimens, %	19.1	46.4	41.0	45.6	42.6	45.2

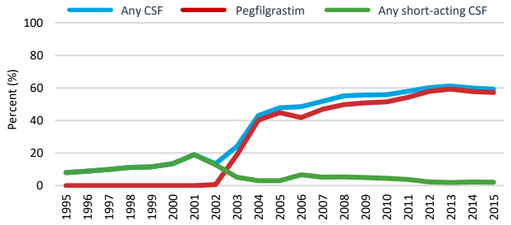
FN = febrile neutropenia.

Figure 1. Type of chemotherapy regimens by FN risk category



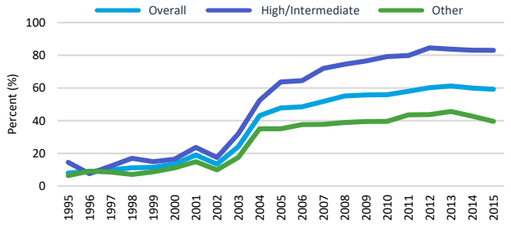
FN = febrile neutropenia.

Figure 2. Use of PP-CSFs for all regimens combined, any CSF and by type of agent



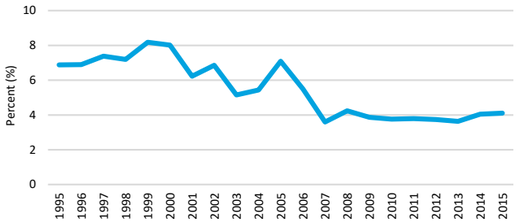
CSF = colony-stimulating factor; PP-CSF = primary prophylaxis with colony-stimulating factor.

Figure 3. Use of PP-CSFs (any agent), overall and by FN risk category



FN = febrile neutropenia; PP-CSF = primary prophylaxis with colony-stimulating factor.

Figure 4. Overall unadjusted incidence (%) of neutropenia-related hospitalization in the first cycle of chemotherapy



Conclusions

- Among older patients diagnosed with NHL receiving myelosuppressive chemotherapy from 1995 to 2015, PP-CSF use increased substantially after 2002
- Over the same 20-year period, incidence of neutropenia-related hospitalization in the first cycle decreased, on average, 6% each year before 2010 and was flat from 2010 onward after controlling for patient characteristics
- Further studies are needed to understand overall decreasing trends in neutropenia-related hospitalization and effects of changes in chemotherapy and FN management

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Disclosures

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