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Febrile Neutropenia as a Marker of an Infectious Phenotype and Poor Long-term Outcomes among Patients Treated with Chemotherapy for Malignant Diseases

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BACKGROUND

- Febrile neutropenia (FN) is a common complication of chemotherapy, associated with increased short-term morbidity and mortality[1-3]
- Literature on possible long-term consequences of FN is limited[4]

Aim of the study

- To examine whether the emergence of FN within the first 6 months from starting chemotherapy identifies individuals with an infectious phenotype thereafter and whether this phenotype was associated with excess mortality

METHODS AND DESIGN

- Retrospective cohort study
- Data were obtained from electronic health records (the PERSIMUNE data repository)

Study population

- Consecutive patients ≥16 years of age, initiating first-line chemotherapy for malignant disease at Copenhagen University Hospital, Denmark, 2010 to 2015
- The cohort was stratified based on history of emerging FN within the first 6 months after starting chemotherapy: no FN, 1 FN episode or >1FN episode

Exposure, outcome and follow-up

- **Exposure:** FN following chemotherapy
- **Outcome:** Collection of a blood culture sample was used as a proxy for infection
- **Baseline:** 6 months after initiation of chemotherapy
- **End of follow-up**: Infection, date of death, initiation of a new course of chemotherapy or September 29th 2015

Statistical Methods

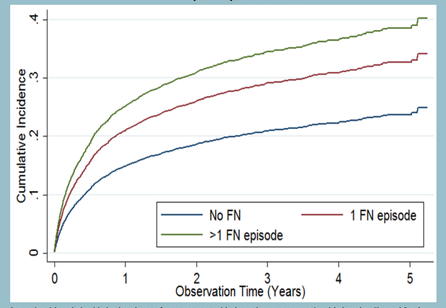
- **Competing risks regression** analysis with death or a new course of chemotherapy as competing events
- **Poisson regression** analysis adjusted for sex, age, diagnosis, calendar year, baseline leucocyte count, hemoglobin, serum albumin, body surface area, comorbidities and stage of disease
- In analyses of mortality, infection was included as a time-updated variable

Table 1 Patient characteristics at baseline

	No FN	1 FN-Episode	>1 FN-Episode	Total population
Total, n (%)	6,454 (100.0)	617 (100.0)	119 (100.0)	7,190 (100.0)
Female n(%)	3,220 (49.9)	362 (58.7)	74 (62.2)	3,656 (50.9)
Age, median (IQR)	64 (54-71)	64 (54-71)	65 (59-72)	64(54-71)
Age groups, n (%)				
<40	422 (6.54)	48 (7.78)	9 (7.56)	479 (6.66)
40-59	2,064 (32.0)	198 (32.1)	26 (21.9)	2,288 (31.8)
60-79	3,675 (56.9)	355 (57.5)	79 (66.4)	4,109 (57.2)
80+	293 (4.54)	16 (2.59)	5 (4.20)	314 (4.37)
Baseline leukocyte count, n (%)				
<3.5	574 (8.89)	78 (12.6)	25 (21.0)	677 (9.42)
3.5-8.8	4,476 (69.4)	418 (67.8)	68 (57.1)	4,962 (69.0)
>8.8	1,404 (21.8)	121 (19.6)	26 (21.9)	1,551 (21.6)
Missing values	0	0	0	0
Baseline hemoglobin, n(%)				
< lower limit of normal*	3,532 (54.7)	398 (64.5)	74 (62.2)	4,004 (55.7)
≥lower limit of normal	2.898 (44.9)	219 (35.5)	42 (35.3)	3,159 (43.9)
Missing values	24 (0.37)	0 (0.00)	3 (2.52)	27 (0.38)
Baseline albumin, n (%)				
< lower limit of normal**	1,492 (23.1)	189 (30.6)	45 (37.8)	1,726 (24.0)
≥lower limit of normal	4,626 (71.7)	406 (65.8)	72 (60.5)	5,104 (71.0)
Missing values	336 (5.21)	22 (3.57)	2 (1.68)	360 (5.01)
Charlsons Comorbidity Index, n (%)				
2	5,167 (80.1)	455 (73.7)	79 (66.4)	5,701 (79.3)
3	448 (6.94)	55 (8.91)	13 (10.9)	516 (7.18)
4+	839 (13.0)	107 (17.3)	27 (22.7)	973 (13.5)
Stage of disease, n (%)				
Adjuvating	1,342 (20.8)	112 (18.2)	15 (12.6)	1,469 (20.4)
Neo-adjuvating/concomitant	2,360 (36.6)	184 (29.8)	18 (15.1)	2,562 (35.6)
Inoperable/Disseminated/Metastatic	2,016 (31.2)	219 (35.5)	51 (42.9)	2,286 (31.8)
Missing/unknown	736 (11.4)	102 (16.5)	35 (29.4)	873 (12.1)

*lower limit for normal haemoglobin level was 8.3 mmol/L for men and 7.3 mmol/L for women
**lower limit for normal albumin level was <36 g/L if age<70 years and <34 g/L if age>70 years

Figure 1 Cumulative incidence of infection in the period from 6 months after inititation of first line chemotherapy, stratified by episodes of febrile neutropenia prior to baseline



Competing risk analysis with death and start of new treatment with chemotherapy as competing risks based on Fine and Gray's proportional subhazards model
FN, Febrile Neutropenia

RESULTS

Characteristics at baseline and follow-up

- We followed 7,190 patients (median age 64 years (IQR, 54-71), 3,656 (50.9%) women **(Table 1)**) with one of 26 types of cancers for a total of 8,486 person-years

Risk of infection

- Overall 1,370 had an infectious event, with incidence rates of 15.3 (95%CI, 14.5-16.2), 24.3 (95%CI, 20.7-28.5) and 26.71 (95%CI, 19.2-37.2) per 100 person-years for those with no, 1 or >1 FN episode, respectively **(Table 2)**
- The relative risk of infection was approximately 2-fold increased among the groups with FN compared with the group with no FN **(Table 2)**
- The cumulative incidences of infection three years after baseline were 21%, 31% and 34% for patients with no, 1 or >1 episode of FN, respectively **(Figure 1)**
- High age, leukocytosis, anemia, hypoalbuminemia, co-morbidities and disseminated disease were individual risk factors for infection **(Table 2)**

Risk of death

- Mortality rates in the time after infection, compared to the time before/without infection, were markedly increased persisting up to six months after the event **(Table 3)**

CONCLUSION

- Febrile neutropenia following chemotherapy is associated with a long-term increased risk of infection
- Patients experiencing an infection were at excess of death from when the event was diagnosed and up to 6 months thereafter

PERSPECTIVES

- Febrile neutropenia is a relevant marker of the infectious phenotype among patients treated with chemotherapy for malignant disease
- Identifying risk factors that can stratify patients with febrile neutropenia in high and low risk of developing subsequent infections could be used to guide the intensity of monitoring of cancer patients treated with common therapy regime

Table 2 Incidence rates of- and risk factors for first infection

	No. of events	IR (95%CI)*	IRR (95%CI)	aIRR(95%)**
FN-groups				
No FN	1,182	0.15 (0.14-0.16)	1 (ref.)	1 (ref.)
1 FN-episode	153	0.24 (0.21-0.28)	1.59 (1.34-1.88)	**1.80 (1.51-2.15)**
>1 FN-episode	35	0.27 (0.19-0.37)	1.75 (1.25-2.44)	**2.10 (1.48-2.98)**
Sex				
Female	567	0.11 (0.10-0.12)	1 (ref.)	1 (ref.)
Male	804	0.23 (0.21-0.25)	2.02 (1.81-2.25)	1.09 (0.95-1.26)
Age groups, n (%)				
<40	63	0.08 (0.06-0.10)	0.71 (0.54-0.93)	1.08 (0.81-1.45)
40-59	347	0.11 (0.10-0.12)	1 (ref.)	1 (ref.)
60-79	892	0.21 (0.20-0.23)	1.97 (1.74-2.23)	**1.18 (1.04-1.35)**
80+	68	0.23 (0.18-0.29)	2.13 (1.64-2.76)	1.23 (0.94-1.62)
Baseline leukocyte count, n (%)				
<3.5	106	0.12 (0.10-0.15)	0.91 (0.74-1.11)	0.77 (0.63-0.95)
3.5-8.8	859	0.13 (0.13-0.14)	1 (ref.)	1 (ref.)
>8.8	405	0.33 (0.30-0.36)	2.41 (2.14-2.72)	**1.90 (1.68-2.14)**
Missing values	0	0	0	0
Baseline hemoglobin, n(%)				
< lower limit of normal*	842	0.20 (0.19-0.21)	1.60 (1.44-1.79)	**1.26 (1.11-1.43)**
≥lower limit of normal	523	0.12 (0.11-0.14)	1 (ref.)	1 (ref.)
Missing values	5	0.16 (0.07-0.38)	1.26 (0.52-3.04)	1.42 (0.55-3.64)
Baseline albumin, n (%)				
< lower limit of normal**	407	0.35 (0.32-0.38)	2.46 (2.19-2.76)	**1.69 (1.48-1.91)**
≥lower limit of normal	943	0.14 (0.13-0.15)	1 (ref.)	1 (ref.)
Missing values	20	0.03 (0.02-0.05)	0.22 (0.14-0.34)	0.58 (0.36-0.96)
Charlsons Comorbidity Index, n (%)				
2	1028	0.14 (0.14-0.15)	1 (ref.)	1 (ref)
3	127	0.27 (0.23-0.32)	1.89 (1.57-2.27)	**1.41 (1.17-1.71)**
4+	215	0.25 (0.22-0.29)	1.74 (1.50-2.02)	**1.26 (1.07-1.47)**
Stage of disease, n (%)				
Adjuvating	141	0.05 (0.04-0.06)	1 (ref.)	1 (ref.)
Neo-adjuvating/concomitant	479	0.18 (0.16-0.19)	3.41 (2.83-4.12)	**2.45 (1.87-3.21)**
Inoperable/Disseminated/Metastatic	530	0.27 (0.24-0.29)	5.17 (4.29-6.23)	**3.88 (3.04-4.95)**
Missing/unknown	220	0.22 (0.19-0.25)	4.19 (3.39-5.18)	4.50 (2.88-7.04)

Univariate and multivariate Poisson regression analyses. All variables were included in the multivariate model, including diagnoses.
*IR, Incidence Rate
**aIRR, adjusted Incidence Rate Ratio

Table 3 Mortality rates in the time after/without infection vs. before infection

Time after infection	MR* (95%CI)	aMRR** (95%CI)
0-1 months	3.35 (3.00-3.74)	7.62 (6.76-8.59)
1-3 months	1.62 (1.46-1.79)	4.20 (3.76-4.70)
3-6 months	0.76 (0.53-1.09)	2.26 (1.57-3.24)
> 6 months	0.28 (0.24-0.33)	1.02 (0.87-1.21)

*MR, Mortality Rate
**aMRR, adjusted Mortality Rate Ratio

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