Febrile neutropenia outside of clinical trials in intermediate-risk patients receiving chemotherapy. A MASCC Neutropenia, Infection and Myelosuppression study group - prospective, real-world study.

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Background

- Neutropenia is a major cause of infection-related morbidity and mortality in patients treated with myelosuppressive chemotherapy regimens [1, 2].
- Current evidence-based guidelines from the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) recommend prophylaxis with G-CSF for patients treated with chemotherapy with an FN risk ≥20%, and for patients receiving chemotherapy with an FN risk of 10% to 20% if they also present with risk factors including age ≥ 65 years, poor performance status and prior FN [2, 5, 8].
- Febrile neutropenia (FN) is the most serious manifestation of neutropenia and a key driver of chemotherapy dose delays and/or reductions, which may impact treatment efficacy [2, 3]. The development of FN often leads to increased treatment costs and longer hospital stays, and may also be associated with reduced quality of life (QoL) [1].
- FN occurs frequently during chemotherapy. In a retrospective cohort study, gFN occurred in 13% to 21% of patients receiving common myelosuppressive chemotherapy regimens for metastatic solid tumours, most frequently during the first cycle (23% to 36%) [4].
- Granulocyte colony-stimulating factors (G-CSFs) can be used prophylactically to reduce the risk, severity and duration of FN, and as an adjunct to support the delivery of dose-dense (increased frequency) or dose-intense (increased dose) myelosuppressive regimens [2, 5].

Methods

Study Design

- This is a prospective, observational, multinational, multicentre study which recruited 371 patients from Dec 2016 – Dec 2019. A total of 6 study sites participated including sites in Belgium, Lebanon, Pakistan, South Africa, Spain and Switzerland.
- Patients are registered through a secure website as soon as they have signed informed consent forms and before the start of chemotherapy. Patients will be observed for the duration of the chemotherapy line (up to 6 cycles and up to 30 days after the last administration of chemotherapy).
- Each patient signed informed consent and institutional ethics approval was obtained from Pharma-Ethics, Pretoria, South Africa (ethics committee working according to the South African Ethics regulations).

Table 1. Patients were assed from the following institutions:

Neutropenia for cycle 1		
Institution	**N =362**	**%**
Hospital Clinic de Barcelona - Spain	151	42
The Medical Oncology Centre of Rosebank – South Africa	86	24
Aga Khan University - Pakistan	60	17
Institut Bordet - Belgium	31	9
Centre hospitalier de l'Université Saint-Joseph - Beyrouth	13	4
Hirslanden Medical Center - Switzerland	12	3
University Hospital Complex Orense - Spain	9	2

Primary Objective

- The primary objective of this real-world study is to estimate the rate of patients who will develop at least one episode of FN (i.e. absolute neutrophil count (ANC) < 0.5 IU and temperature ≥ 38.5 °C) when treated with a chemotherapy regimen (new chemotherapy line) expected to be associated with a moderate (10% to 20%) risk of FN, according to published guidelines.

Study Objective

- Secondary outcome measures include overall incidence of FN after all chemotherapy cycles, incidence of complicated FN after each chemotherapy cycle, all cycles rates.
- The incidence of grade 4 neutropenia.
- The incidence of relative dose intensity decreases and/or delays, and if particular risk factors can be contributed to this.

Eligibility

Eligible patients are those who meet the following criteria:

Inclusion criteria

1. Diagnosis of a solid tumor or Hodgkin's disease or non-Hodgkin's lymphoma
2. Age > 18 years
3. Planned administration of a chemotherapy line to be started during the study period of accrual (any line of chemotherapy, any setting: adjuvant or metastatic)
4. Expected risk of febrile neutropenia according to published guidelines (ASCO, EORTC, NCCN) in the range of 10% to 20% (a list of acceptable regimens with doses and administration schedules will be published before study start, continuously updated during the conduct of the study and always be available online once the study will be opened for accrual)
5. No planned administration of growth factors
6. No previous inclusion in the study for another chemotherapy line
7. Written informed consent (depending on local context)
8. Patient willingness to fill in QoL questionnaires on days 1 and 8 of first chemotherapy cycle as well as compliance for blood sampling on the same days (for selected participating institutions only)

Exclusion criteria

9. Exclusion criteria
10. Patients scheduled to receive a chemotherapy regimen not belonging to the acceptable list of regimens
11. Patients receiving FN primary prophylaxis with antibiotics
12. Patients with any haematological malignancy other than Hodgkin's Disease or Non-Hodgkin's Lymphoma are not eligible.
13. Prior treatment with high dose chemotherapy and/or stem cell transplantation
14. Patients with Abnormal Kidney (Creatinine more than X 1.5 upper limit normal) and Liver Function (ASAT and ALAT more than X 2 upper limit normal)

Patient Characteristics

- In total we evaluated 362 patients receiving 1601 cycles of chemotherapy.

Table 2. Patient Characteristics.

Age		
Median Age	52	
Range	18-83	
Gender		
	Total	**%**
Female	225	66%
Male	115	34%
Underlying cancer		
	Total	**%**
Breast cancer	175	51%
Colorectal cancer	112	33%
Non Hodgkin's lymphoma	17	5%
Prostate cancer	16	5%
Germ cell tumor	9	3%
Non small cell lung cancer	6	2%
Gastric cancer	3	1%
Oesophageal cancer	2	1%
Metastatic disease		
	Total	**%**
No	240	71%
Yes	100	29%
Charlson score		
Median	3	
Range	0-14	
Weight loss		
	Total	**%**
<5%	265	78%
Between 5% and 10%	24	7%
>10%	25	7%
Unknown	26	8%

Results

Table 3. Chemotherapy treatments.

Number of cycles received		
	Total	**%**
Median	4 cycles	
Number of patients with 4 cycles	152	45%
Number of patients with 6 cycles	121	36%
No chemotherapy given	2 patients	
Reason for stopping follow-up		
	Total	**%**
Chemotherapy complete	312	92%
Lost to follow-up	8	2%
Patient died	6	2%
Other reason	14	4%
Number of cycles with		
	Total	**%**
- Dose reduction	166	11%
- Delay in chemotherapy administration	219	15%
Number of patients		
	Total	**%**
- Dose reduction	75	22%
- Delay in chemotherapy administration	146	43%

Table 4. Neutropenia and Febrile Neutropenia Incidence.

Neutropenia for cycle 1	
	Totals and %
Grade 1	11 (3%)
Grade 2	12 (4%)
Grade 3	16 (5%)
Grade 4	38 (11%)
Grade 1 to Grade 4 Total	77 (23%)
Neutropenia for all cycles	
	Totals and %
Grade 1	76 (22%)
Grade 2	64 (19%)
Grade 3	59 (17%)
Grade 4	73 (21%)
Grade 4 in at least 1 cycle	56 (16%)
Febrile Neutropenia	
	Totals and %
Cycle 1	19 (6%)
Total episodes for all cycles	42 (13%)
All cycles in at least 1 cycle	32 (9%)

Figure 1. Incidence of Neutropenia.

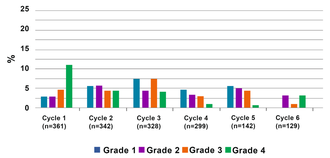

Figure 2. Incidence of Febrile Neutropenia.

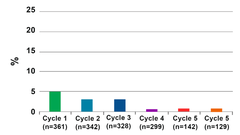

Figure 3. All grades neutropenia.

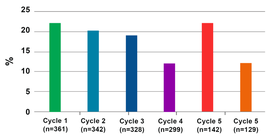

Table 5. Rate of Grade 4 Neutropenia.

Rate of Grade 4 Neutropenia (95% CI)		
Cycle 1 (n=361)	11	(8-14)
Cycle 2 (n=342)	4	(2-7)
Cycle 3 (n=328)	4	(2-6)
Cycle 4 (n=299)	1	(0.2-3)
Cycle 5 (n=142)	1	(< 1-4)
Cycle 6 (n=129)	3	(< 0.1-8)

Table 6. Rate of Febrile Neutropenia.

Rate of Febrile Neutropenia (CI 95%)		
Cycle 1 (n=361)	5	(3-8)
Cycle 2 (n=342)	3	(1-5)
Cycle 3 (n=328)	3	(1-5)
Cycle 4 (n=299)	<1	(< 1-2)
Cycle 5 (n=142)	<1	(< 1-4)
Cycle 6 (n=129)	<1	(<1-4)

Table 7. All grades neutropenia (CI 95%).

All grades neutropenia (CI 95%)		
Cycle 1 (n=361)	22	(17-26)
Cycle 2 (n=342)	20	(16-25)
Cycle 3 (n=328)	19	(15-24)
Cycle 4 (n=299)	12	(9-16)
Cycle 5 (n=142)	22	(10-23)
Cycle 6 (n=129)	7	(3-13)

- The rate of patients with at least one episode of grade 4 neutropenia is 15% (95% CI : 12%-20%).

Table 8. Outcome of febrile neutropenia by the MASCC index.

	MASCC Score	Number of patients
High risk	14	1
	15*	2
	18*	3
	19	1
	20	7
Low risk	21	4
	22	2
	23	5
	24	9
	26	8

* Serious complication.

- Forty-two episodes of febrile neutropenia were documented. Those 42 episodes occurred in 32 patients.
- Outcome of neutropenia by the MASCC index.
- Fourteen patients (33%) had poor risk vs 28 (67%) patients with a good risk.
- Two patients (5%) in the 'poor risk' group (MASCC score 15 and 18) developed a serious complication.
- There were no mortalities reported related to febrile neutropenia.

Table 9 Risk Index Table.

Characteristic	Weight
Burden of febrile neutropenia with no or mild Symptoms[a]	5
No hypotension (systolic BP > 90mm Hg)	5
No chronic obstructive pulmonay disease[b]	4
Solid tumor or hematological malignancy with no previous fungal infection[c]	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms[a]	3
Outpatient status	3
Age <60 years	2

[a] Burden of febrile neutropenia refers to general clinical status as influenced by the febrile neutropenic episode. It is evaluated in accordance with the following scale: no symptoms (5), mild symptoms (5), moderate symptoms (3), severe symptoms (0), moribund (0).

[b] Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in FEVs, need for oxygen therapy and/or steroids and/or bronchodilators.

[c] Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

[d] The points attributed to the variable "burden of febrile neutropenia" are not cumulative. Thus, the maximum theoretical score is therefore 26. A score of ≥ 21 is considered low risk and a score of < 21 as high risk (positive predictive value of 91%, specificity of 68%, and sensitivity of 71%).

https://www.mascc.org/mascc-fn-risk-index-score

Conclusions

- Febrile neutropenia and grade 4 neutropenia remains a significant problem in cancer intermediate-risk patients undergoing chemotherapy treatment. The relative dose intensity (either reductions or delays) was affected 26% of patients (see paper).
- This study was limited to patients receiving intermediate risk chemotherapy regimes (expected incidence of FN 10 – 20%).
- The incidence of neutropenia was 22%.
- The incidence of grade 4 neutropenia was 11%.
- The rate of patients with at least one episode of grade 4 neutropenia is 15%.
- The overall incidence FN was 11%, with half of these episodes occurring during the first cycle.
- The serious medical complication rate on this intermediate risk group of patients was low.
- Intermediate risk patients with well-known, previously reported risk factors could be considered for primary prophylaxis with GCSF.

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ESMO Virtual Congress 2020; September 19 - 22, 2020

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