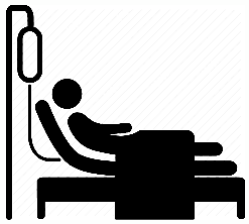

Development of a comprehensive risk scoring system for prediction of chemotherapy-induced severe neutropenia

Bahram Mofid, M.D

Professor of Radiation Oncology

Department of Radiation Oncology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Disclosure Statement

- The authors have no relevant relationships to disclose.
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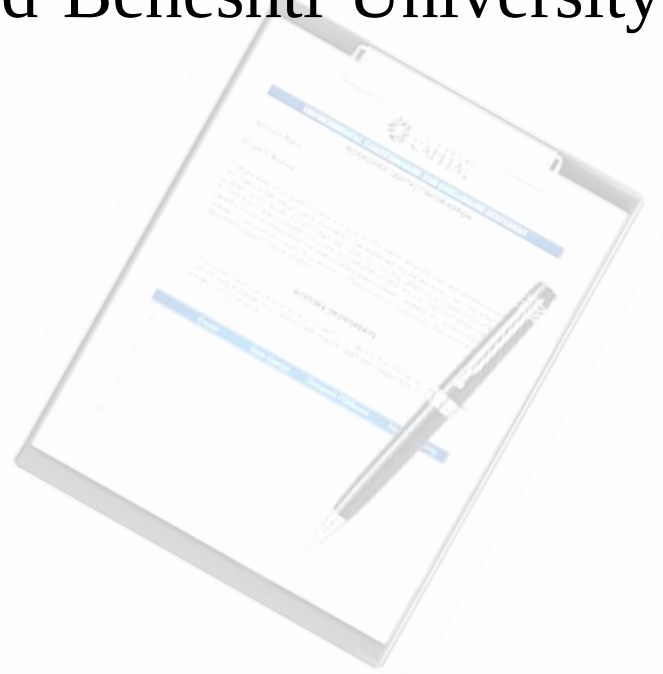


Problem statement

- ✓ Neutropenia is the major **dose-limiting toxicity** of chemotherapy.
- ✓ Neutropenic events can be associated with **morbidity**, **mortality** and **cost**.
- ✓ There is surprisingly **no** suitable **prediction rule** for this toxicity in use today.
- ✓ There is a serious need to develop a **comprehensive**, **simple**, **sensitive and specific** scoring system for prediction of this important complication.

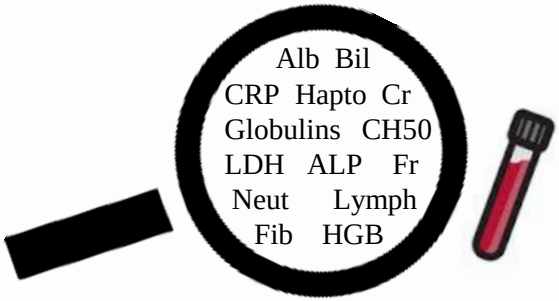
Aim:

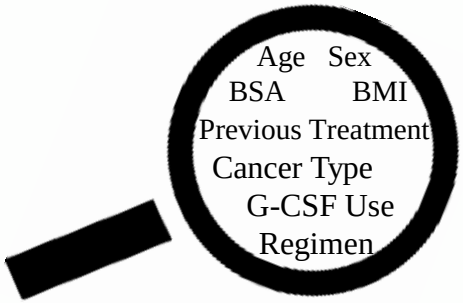
Preliminary development of a prediction rule for identifying patients at risk for severe neutropenia **(ANC <500/mm3)**

Patients & Methods

Data collection:

- 212 Patients with solid tumors or lymphoma were included in our study.
- Laboratory& clinical independent variables were prospectively collected.
- Regular nadir CBCs were obtained in the first treatment cycle.
- Patients without CBC count at day 10-14 were excluded.





All chemotherapy regimens were graded according to the best guidelines

1- Low-risk

2- Intermediate-risk

3- High-risk

NCCN National Comprehensive Cancer Network®

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

EORTC The future of cancer treatment

ASCO®

1ST FIRST TIME

No previous studies have used this classification

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Examples of Disease Settings and Chemotherapy Regimens with a High Risk for Febrile Neutropenia (>20%)

- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-B)
- *This list is not comprehensive*; there are other agents/regimens that have a high risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)

Acute Lymphoblastic Leukemia (ALL)
- ALL induction regimens (See NCCN Guidelines for ALL)

Bladder Cancer
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)[1]

Breast Cancer
- Docetaxel + trastuzumab (metastatic or relapsed)[2]
- Dose-dense AC followed by T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)[3]
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)[4]

Esophageal and Gastric Cancers
- Docetaxel/cisplatin/fluorouracil[5]

Hodgkin Lymphoma
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[6]

Kidney Cancer
- Doxorubicin/gemcitabine[7]

Non-Hodgkin's Lymphomas
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapsed/refractory)[8,9]
- ICE (ifosfamide, carboplatin, etoposide) (DLBCL, PTCL, 2nd line, salvage)[10]
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)[11]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab[12,13]
- MINE (mesna, ifosfamide, novantrone, etoposide) (DLBCL, PTCL, 2nd line, refractory)[14]
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd line)[15]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (DLBCL, PTCL, 2nd line, recurrent)[16]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[17,18]

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)[19]
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)[19]

Myelodysplastic Syndromes
- Antithymocyte globulin, rabbit/cyclosporine[20]

Ovarian Cancer
- Topotecan[21]
- Paclitaxel[22]
- Docetaxel[23]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[24]
- Doxorubicin[25]
- Ifosfamide/doxorubicin[26]

Small Cell Lung Cancer
- Topotecan[27]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[28]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)[29,30]
- TIP (paclitaxel, ifosfamide, cisplatin)[31]

*In general, dose-dense regimens require growth factor support for chemotherapy administration.

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 4)

See Chemotherapy Regimen References, MGF-A (3 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Statistical Methods

Developing a predictive model:

Forward stepwise multivariate logistic regression analysis

Internal Validation:

Bootstrapping

Deriving a Scoring System:

1- The regression coefficients were divided by the smallest coefficient

2- The obtained number rounded to the nearest integer

3- Each individual risk score of the 6 predictors of a patient should be added

Patients with a total risk score of **≥3** were expected to experience severe neutropenia

Results

- Data from **212** patients were prospectively collected
- **153** patients were included in the final analysis
- **26** patients experienced grade 4 neutropenia

Characteristics of components in multivariate model

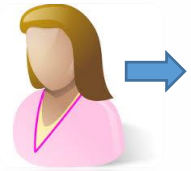
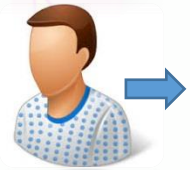
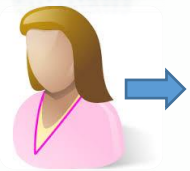
Predictor	Odds Ratio	Regression Coefficient	P-value	Score
High-Risk Regimen without prophylactic G-CSF	36.59	3.6	<0.001	2
Intermediate-Risk Regimen without prophylactic G-CSF	8.09	2.09	0.011	1
GFR <60	27.66	3.32	<0.001	2
Abnormal Ferritin	4.9	1.59	0.020	1
Elevated Haptoglobin	5.69	1.73	0.030	1
BMI under 23	4.73	1.55	0.027	1

Characteristics of scoring system

Observed		Predicted [a]		
		Severe Neutropenia		ROC 0.845
		No	Yes	
Severe Neutropenia	No	117	10	Specificity 92.1%
	Yes	6	20	Sensitivity 76.9%
a. The cut-off score is ≥3 b. Negative predictive value c. Positive predictive value		NPV [b] 95.1%	PPV [c] 66.5%	Accuracy 89.5%

Examples

EXAMPLE

	Regimen (Score)	GFR (Score)	Ferritin (Score)	Haptoglobin (Score)	BMI (Score)	Total Score	Expected Neutropenia
	AC-3w (1)	80 (0)	303 (1)	261 (1)	26 (0)	3	**Yes**
	BEP (2)	76 (0)	691 (1)	55 (0)	21.9 (1)	4	**Yes**
	EC+ G-CSF (0)	52 (2)	55 (0)	187 (0)	25 (0)	2	**No**

Discussion

Comparison of characteristics with other studies

Study	Event	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative predictive value (%)	Overall Accuracy (%)	Cancer Type
LÓPEZ-POUSA et al. (2010)	Grade 3&4 Neutropenia	63	67	17	94	67	Solid tumors
Moreau et al. (2009)	Febrile Neutropenia	78.6	62.3	42.7	89.1	66.6	Hematologic cancers
Our Study	Grade 4 Neutropenia	76.9	92.1	66.6	95.1	85.5	Solid tumors & Lymphoma

Limitations of our study:

- Single-center design of study
- Small number of events (26 severe neutropenia)
- Events are just related to the first cycle of the treatment

Conclusion

Our prediction rule may confer multiple advantages over other rules

- ✓ **Comprehensive**
- ✓ **simple-to-compute**
- ✓ **Accurate (sensitive & specific)**
- ✓ **Using cost-effective & accessible laboratory tests**

- ➢ *This scoring system may be useful in better management of patients.*
- ➢ *Further studies are required.*

Thanks for your attention

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