Profilassi in corso di terapia con i nuovi farmaci nel mieloma

Torino 04.10.2018

Massimo Pini

SSD Ematologia e Malattie Trombotiche

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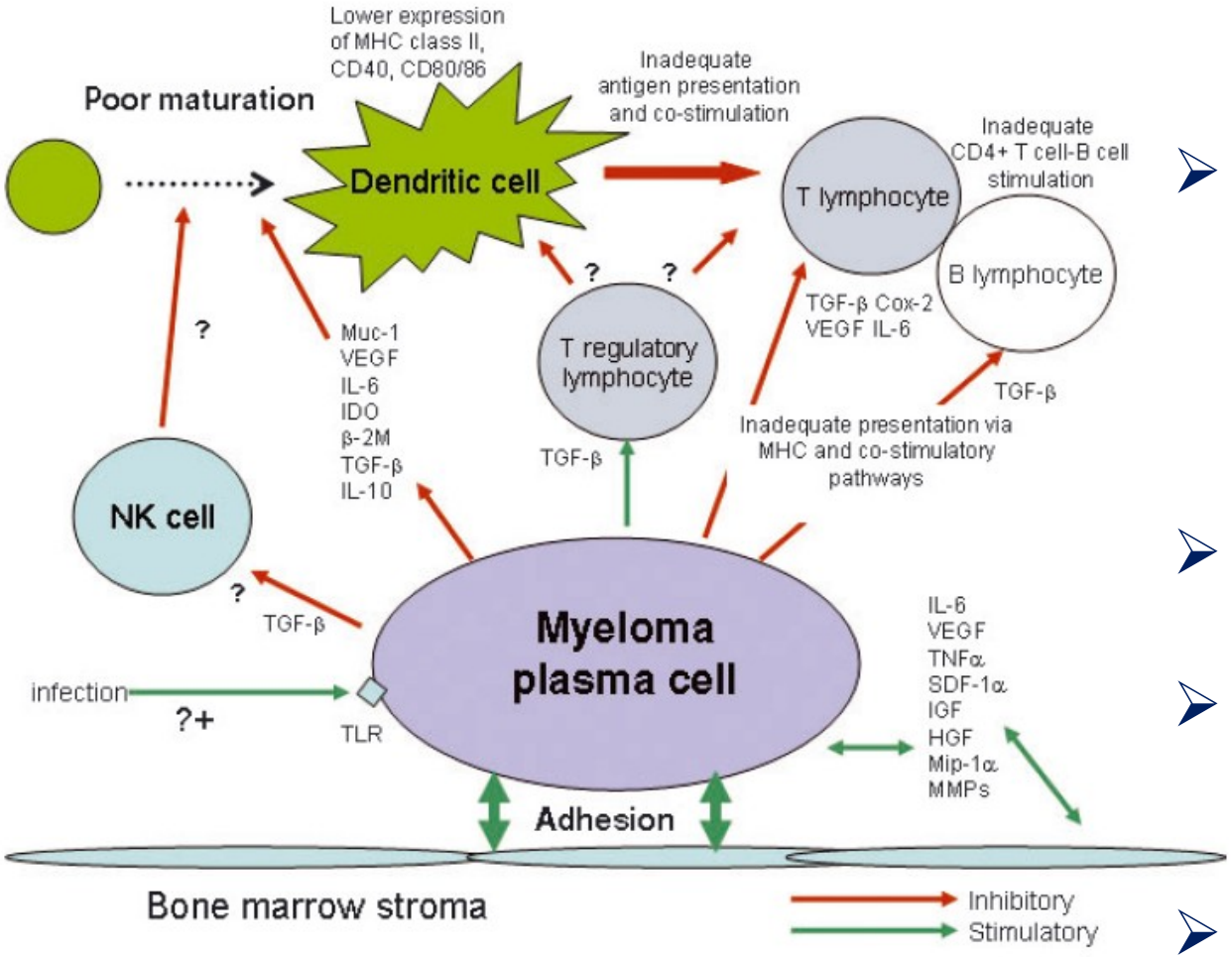
Le infezioni rappresentano un' importante causa di mortalità e morbidità nel MM

- ipogammaglobulnemia
- Disregolazione della funzione linfocitaria
- Effetto immunodepressivo iatrogeno in particolare degli steroidi
- Neutropenia correlata all' infiltrazione midollare o all' effetto dei farmaci

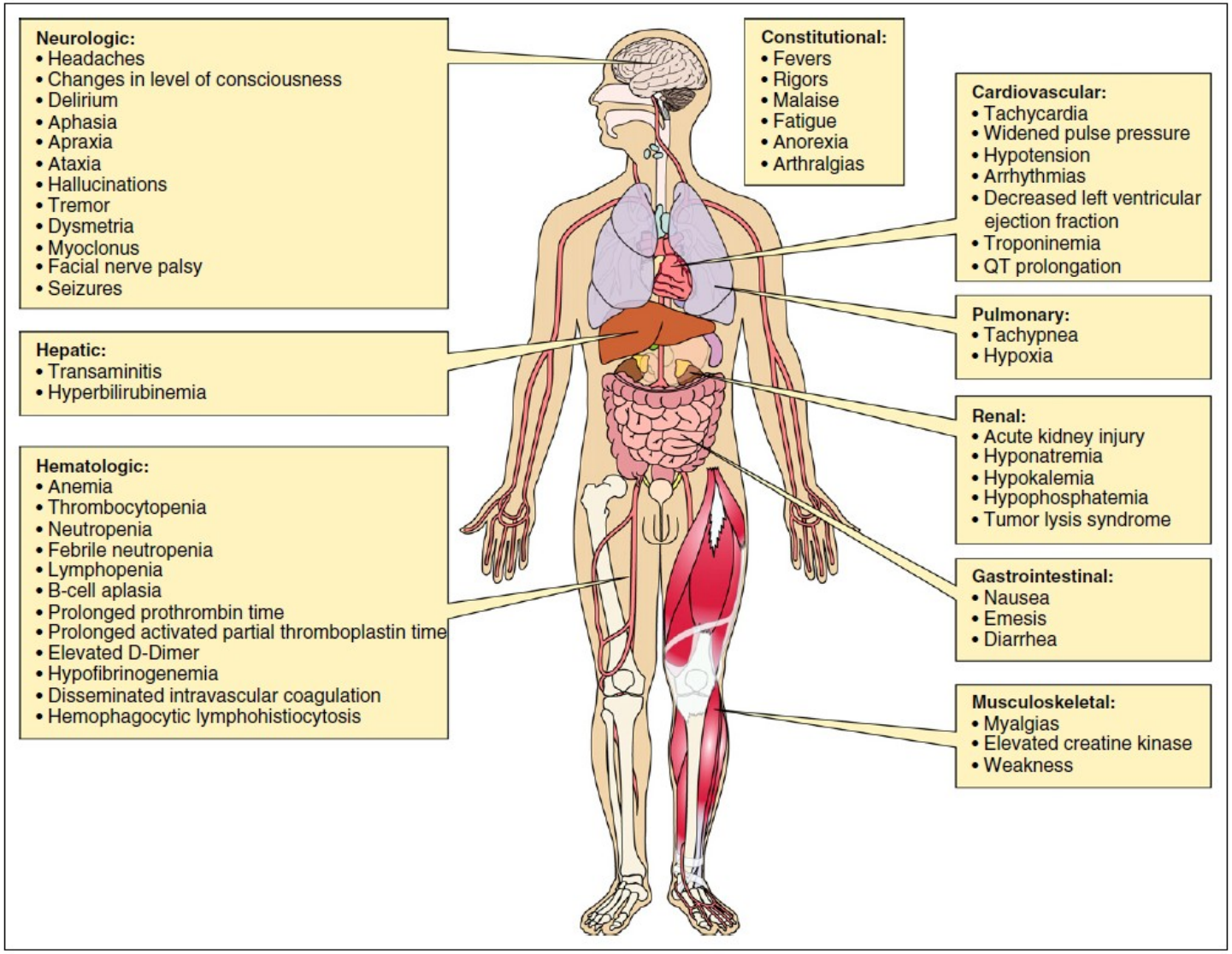
Immunodeficienza nel mieloma



- Promuove la sopravvivenza e la crescita delle plasmacellule
- Angiogenesi
- Resistenza alla terapia
- Alterazioni del metabolismo osseo

British Journal of Haematology, 138, 563–579 2007

La speranza di una ridotta tossicità con i nuovi farmaci (realtà-speranza-illusione)



		Teratogenicity	Peripheral neuropathy	Cardiac toxicity	Seizures	Thromboembolic events/DVT	Thrombocytopenia	Hemorrhage	Neutropenia	Anemia	Amenorrhea	Infections	Viral reactivation	Somnolence/drowsiness	Dizziness	Hypotension	Hypertension	Nausea	Vomiting	Diarrhea	Constipation	SPM	Syncope/bradycardia	Infusion reaction	Severe skin reactions	Allergic/hypersensitivity reactions	Hepatic toxicity	Renal toxicity	Edema	Tumor lysis syndrome	Thyroid disorders	Cataract	Pulmonary disorders	Dyspnoea	PML	PRES
IMiDs	Thalidomide	•	•	•	•	•	•		•		•	•	• [a]	•	•							•	•		•	•			•	•						
	Lenalidomide	•	• [b]	•		•	•		•			•										•			•	•			•		•					
	Pomalidomide	•	• [c]	•		•	•		•	•		•			•							•				•	•		•			•				
PIs	Bortezomib	•	•	•	•		•		•	•			• [a]			•		•	•	•	•						•		•				•	•	•	•
	Carfilzomib	•		•		• [c]	•	•									•							•			•	•	•				•	•		•
	Ixazomib	•	•				•											•	•	•	•				•		•		•							
HDACi	Panobinostat	•		•			•	•	•	•		•						•	•	•	•						•				•					
mABs	Elotuzumab								•			•										•		•			•									
	Daratumumab						•		•				•											•													

Annals of Hematology (2018) 97:387–400
https://doi.org/10.1007/s00277-017-3191-7

REVIEW ARTICLE

Incidence of neutropenia and use of granulocyte colony-stimulating factors in multiple myeloma: is current clinical practice adequate?

Xavier Leleu[1] · Francesca Gay[2] · Anne Flament[3] · Kim Allcott[4] · Michel Delforge[5]

Table 1: Traditional and novel agents for RRMM

Agent	Category	Target point	Approval year by FDA
Traditional agents			
Lenalidomide	IMiD	NA	2005
Bortezomib	PI	26S proteasome	2003
Dexamethasone	Glucocorticoid	NA	NA
Novel agents			
Elotuzumab	mAb	SLAMF7	2015
Daratumumab	mAb	CD38	2015
Panobinostat	HDAC- inhibitor	HDAC	2015
Ixazomib	PI	Peptide boronic acid proteasome	2015
Carfilzomib	PI	Epoxyketone proteasome	2013
Pomalidomide	IMiD	NA	2013

Il rischio di infezioni gravi aumenta in modo significativo per valori di neutrofili < 500 cells/microL ed è maggiore se la durata della neutropenia è > di 7 days giorni

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

Table 3. Most Common Adverse Events during Treatment in the Safety Population.*

Event	Daratumumab Group (N=283)		Control Group (N=281)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Hematologic adverse event				
Neutropenia	168 (59.4)	147 (51.9)	121 (43.1)	104 (37.0)
Febrile neutropenia	16 (5.7)	16 (5.7)	7 (2.5)	7 (2.5)

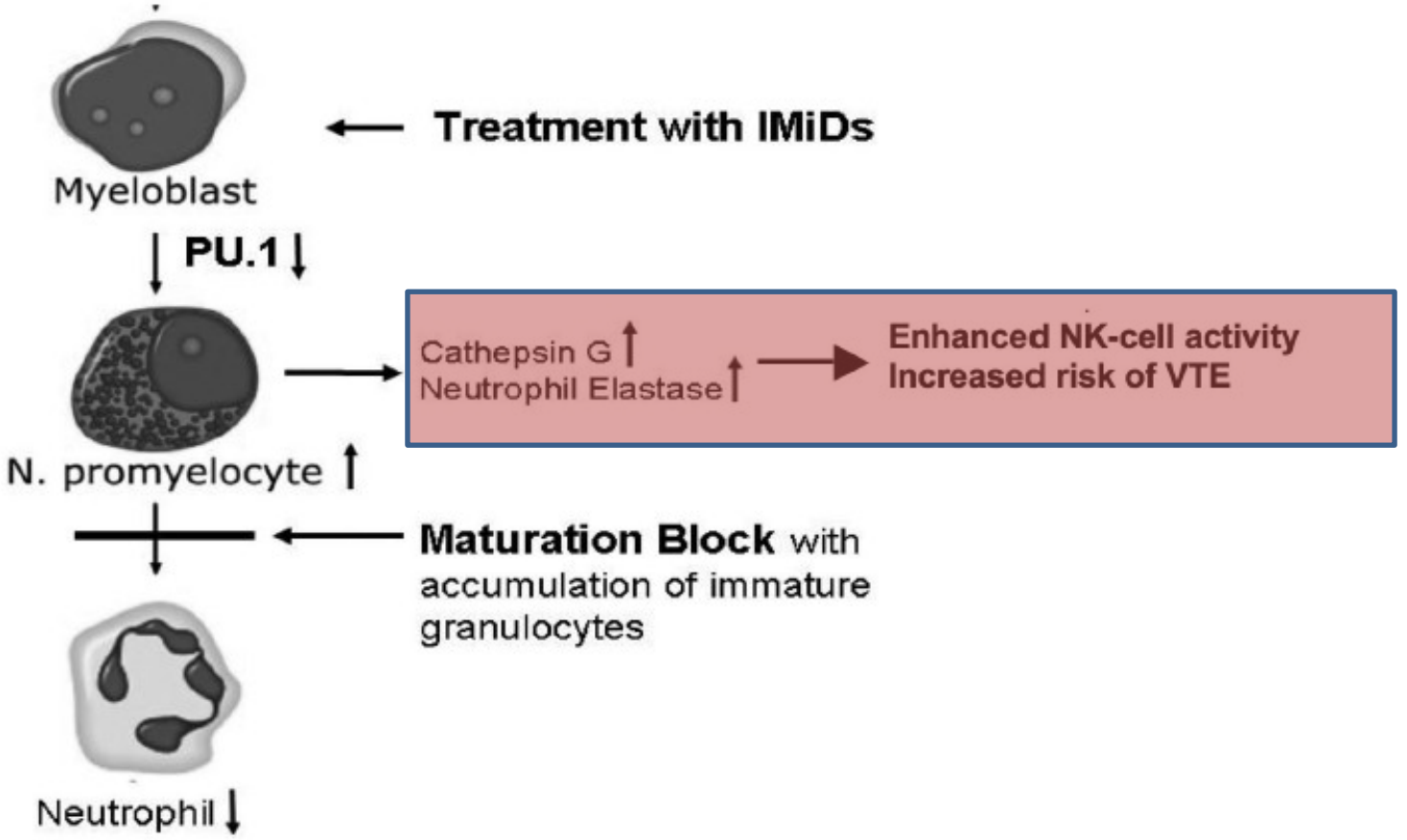
Cyclic ADP-ribose production by CD38 regulates intracellular calcium release, extracellular calcium influx and chemotaxis in neutrophils and is required for bacterial clearance *in vivo*

SANTIAGO PARTIDA-SÁNCHEZ[1], DEBRA A. COCKAYNE[2], SIMON MONARD[1], ELAINE L. JACOBSON[3], NORMAN OPPENHEIMER[4], BETH GARVY[5], KIM KUSSER[1], STEPHEN GOODRICH[1], MAUREEN HOWARD[6], ALLEN HARMSEN[7], TROY D. RANDALL[1] & FRANCES E. LUND[1]

- **CD38 controls neutrophil chemotaxis to bacterial chemoattractants through its production of cyclic ADP-ribose, and acts as a critical regulator of inflammation and innate immune responses.**

Immunomodulatory derivatives induce PU.1 down-regulation, myeloid maturation arrest, and neutropenia

Rekha Pal,[1] Sara A. Monaghan,[2] Andrea Cortese Hassett,[3] Markus Y. Mapara,[1] Peter Schafer,[4] G. David Roodman,[1] Margaret V. Ragni,[1,3] Lynn Moscinski,[5] Alan List,[6] and Suzanne Lentzsch[1]



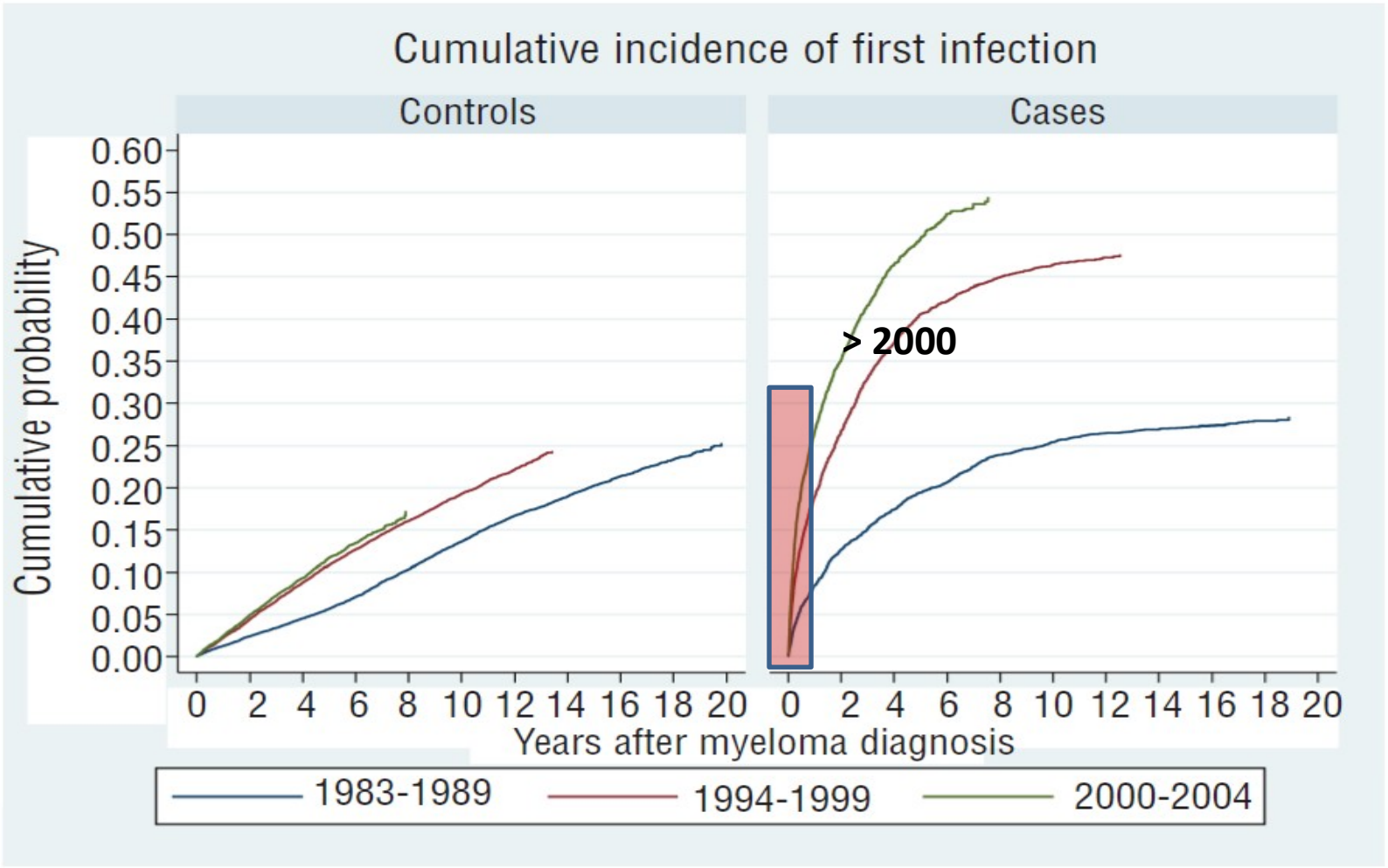
Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients

Cecilie Blimark,[1] Erik Holmberg,[2] Ulf-Henrik Mellqvist,[1] Ola Landgren,[3] Magnus Björkholm,[4] Malin Hultcrantz,[4] Christian Kjellander,[4] Ingemar Turesson,[5] and Sigurdur Y. Kristinsson[4,6]

Haematologica | 2015; 100(1)

Table 2. Relative risk of selected infections after diagnosis of myeloma compared to matched controls.

Disease	Total			One-year follow up		
	Myeloma (n=9 253)	Controls (n=34 931)	HR* (95%CI)	Myeloma	Controls	HR (95%CI)
Any infection (combined)**	3781	6519	7.1 (6.8-7.4)	1626	672	11.6 (10.6-12.7)
Specific infections						
Bacterial***	3361	5792	7.1 (6.8-7.4)	1388	574	11.5 (10.4-12.7)
Pneumonia	2150	3504	7.7 (7.2-8.1)	770	279	12.7 (11.1-14.6)
Osteomyelitis	37	100	3.5 (2.4-5.2)	19	12	6.9 (3.4-14.3)
Septicemia	1336	960	15.6 (14.3-17.1)	464	69	29.9 (23.2-38.6)
Pyelonephritis	152	570	2.9 (2.4-3.5)	50	51	4.3 (2.9-6.4)
Cellulitis	164	564	3.0 (2.5-3.6)	47	58	3.7 (2.5-5.4)
Meningitis	51	28	16.6 (10.2-27.1)	12	3	17.3 (4.9-61.3)
Endocarditis	35	73	5.3 (3.4-8.1)	12	6	8.7 (3.3-23.1)
Viral****	607	556	10.0 (8.9-11.4)	215	54	17.6 (13.1-23.8)
Influenza	150	245	6.1 (4.9-7.6)	52	22	10.5 (6.4-17.3)
Herpes zoster	282	171	14.8 (12.1-18.2)	92	16	25.8 (15.2-43.8)


Cumulative incidence of first infection
Controls
Cases
Cumulative probability
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
> 2000
0 2 4 6 8 10 12 14 16 18 20
0 2 4 6 8 10 12 14 16 18 20
Years after myeloma diagnosis
1983-1989
1994-1999
2000-2004

ORIGINAL ARTICLE

Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma

Lotfi Benboubker, M.D., Meletios A. Dimopoulos, M.D., Angela Dispenzieri, M.D., John Catalano, M.D., Andrew R. Belch, M.D., Michele Cavo, M.D., Antonello Pinto, M.D., Katja Weisel, M.D., Heinz Ludwig, M.D., Nizar Bahlis, M.D., Anne Banos, M.D., Mourad Tiab, M.D., Michel Delforge, M.D., Jamie Cavenagh, M.D., Catarina Geraldes, M.D., Je-Jung Lee, M.D., Christine Chen, M.D., Albert Oriol, M.D., Javier de la Rubia, M.D., Lugui Qiu, M.D., Darrell J. White, M.D., Daniel Binder, M.D., Kenneth Anderson, M.D., Jean-Paul Fermand, M.D., Philippe Moreau, M.D., Michel Attal, M.D., Robert Knight, M.D., Guang Chen, Ph.D., Jason Van Oostendorp, M.Sc., Christian Jacques, M.D., Annette Ervin-Haynes, D.O., Hervé Avet-Loiseau, M.D., Cyrille Hulin, M.D., and Thierry Facon, M.D., for the FIRST Trial Team*

Table 3. Grade 3 or 4 Adverse Events.

Event	Continuous Lenalidomide–Dexamethasone (N=532)	Lenalidomide–Dexamethasone for 18 Cycles (N=540)	MPT (N=541)
Neutropenia	148 (28)	143 (26)	243 (45)
Infection	154 (29)	118 (22)	93 (17)

Terapia antibiotica profilattica e nuovi farmaci

E’ indicata una terapia antibiotica profilattica a fronte del rischio di neutropenia e di infezioni??

Published in final edited form as:
Leukemia. 2012 December ; 26(12): 2517–2520. doi:10.1038/leu.2012.124.

Oral antibiotic prophylaxis of early infection in multiple myeloma: a URCC/ECOG randomized phase III study

DH Vesole[1], MM Oken[2], C Heckler[3], PR Greipp[4], MS Katz[5], S Jacobus[6], and GR Morrow[3] on behalf of the University of Rochester Cancer Center and the Eastern Cooperative Oncology Group

- This study evaluated the impact of prophylactic antibiotics on the incidence of serious bacterial infections (SBIs) during the first 2 months of treatment in patients with newly diagnosed MM. Patients with MM receiving **initial chemotherapy** were randomized on a 1:1:1 basis to daily ciprofloxacin (C; 500 mg twice daily), trimethoprim-sulfamethoxazole (T; DS twice daily) or observation (O)

- **prophylactic antibiotics did not decrease the incidence of serious bacterial infection (⩾grade 3) within the first 2 months of treatment.**

- **routine use of prophylactic antibiotics should not be mandated for patients receiving induction chemotherapy.**

Clinical Microbiology and Infection 24 (2018) S95–S107

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Infezioni Virali

Narrative review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors)

G. Redelman-Sidi [1,*], O. Michielin [2], C. Cervera [5], C. Ribi [3], J.M. Aguado [6,7], M. Fernández-Ruiz [6,7], O. Manuel [4]

Summary of infection risks associated with use of reviewed targeted agents

Agent	Pathway affected	Current indications	Increased risk of infection	Observations
Bortezomib, carfilzomib, ixazomib	Ubiquitin proteasome pathway	MM, relapsed or refractory mantle-cell lymphoma	Major	• Increased risk of HZ and respiratory tract infections (including pneumonia). • Likely increased risk of influenza-related complications.
Bortezomib, carfilzomib, ixazomib	No	May be considered for selected MM patients with additional risk factors (i.e. prolonged high-dose corticosteroid therapy)	Yes	Live attenuated varicella vaccination for VZV-seronegative patients without history of varicella (at least 1 month before starting therapy); HZ/su may be considered for VZV-seropositive patients aged ≥50 years; seasonal TIV (at least 2 weeks before starting therapy and annually thereafter); completed pneumococcal vaccination series (PCN7 or PCN13 followed by PPV23) (at least 2 weeks before starting therapy) with revaccination 5 years later with PPV23	• Antiviral prophylaxis with (val)acyclovir for VZV-seropositive patients during induction therapy and for at least 4 weeks after discontinuation.

Clinical Microbiology and Infection 24 (2018) 583–594

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4)

L. Drgona [1], C. Gudiol [2], S. Lanini [3], B. Salzberger [4], G. Ippolito [3], M. Mikulska [5,*]

Table 3
Summary of risk of infectious complications and possible management strategies for the reviewed targeted agents

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+/HBsAg-antiHBc+)	Risk of CMV infection (monitoring warranted)
CD38-targeted agents	Daratumumab (no data yet available for isatuximab)	Yes	Yes (VZV)	Possible (consider if concomitant corticosteroid therapy)	Possible (consider if concomitant corticosteroid therapy)	No
CD319-targeted agents	Elotuzumab	No	Yes (especially VZV)	Possible (consider if concomitant corticosteroid therapy)	ND (patients received standard prophylaxis for multiple myeloma)	No

Anti-herpesvirus prophylaxis with (val) acyclovir should be administered to VZV-seropositive patients at least 1 week before starting daratumumab therapy and for at least 12 weeks after its discontinuation. Seasonal influenza vaccination should be encouraged, when feasible, in patients treated with daratumumab

Ann Hematol (2016) 95:1465–1472
DOI 10.1007/s00277-016-2742-7

ORIGINAL ARTICLE

Incidence and clinical background of hepatitis B virus reactivation in multiple myeloma in novel agents' era

Yutaka Tsukune[1] · Makoto Sasaki[1] · Takeshi Odajima[2] · Atsushi Isoda[3] · Morio Matsumoto[3] · Michiaki Koike[4] · Hideto Tamura[5] · Keiichi Moriya[5] · Shigeki Ito[6] · Maki Asahi[7] · Yoichi Imai[8] · Junji Tanaka[8] · Hiroshi Handa[9] · Hiromi Koiso[10] · Sakae Tanosaki[11] · Jian Hua[12] · Masao Hagihara[12] · Yuriko Yahata[1] · Satoko Suzuki[13] · Sumio Watanabe[14] · Hiroki Sugimori[15] · Norio Komatsu[1]

EPATITE VIRALE

- **Riattivazione in pazienti AbHBs+/AbHBc**

- **Fra i pz.esposti all'HBV (AbHBs/AbHBc) senza terapia profilattica la riattivazione HBV (comparsa di HBV-DNA) risultava :**

  - **8% a 12 mesi**
  - **15% a 24 mesi**

- **Circa il 6% delle riattivazioni riguarda pazienti non sottoposti a ASCT ma trattati (IP, IMIDs)**

HBV

- Patients living in regions with high prevalence of hepatitis as well as those with increased alanine transaminase should be screened (HBsAg, anti- HBc, and anti-HBs)
- Preemptive antiviral prophylaxis with nucleoside/nucleotide analogs should be considered in patients with latent or previous HBV infection

HCV

- Formal recommendation for those with a high risk of HCV infection or with previous infections are not available, but it seems reasonable to screen the high risk group (anti-HCV and/or HCV RNA) and to treat those with evidence of active infection with modern direct-acting antivirals

Clin Exp Immunol 1994; 97 (Suppl 1):21–24

The use of intravenous immune globulin in multiple myeloma

H. M. CHAPEL & M. LEE* *Department of Immunology, John Radcliffe Hospital, Oxford, UK, and *Baxter Biotech Group, Hyland Division, Glendale, California, USA*

IVIG can be given safely to selected patients with multiple myeloma in a stable phase of the disease. Immune globulin protects against life-threatening infections and significantly reduces the risk of recurrent infections. **unico studio controllato randomizzato**

The role of intravenous immunoglobulins (IVIG) prophylaxis in hypogammaglobulinemic patients with lymphoproliferative disorders (LPD) and plasma cell dyscrasias (PCD) has not been established

VOLUME 27 · NUMBER 5 · FEBRUARY 10 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Immunoglobulin Prophylaxis in Hematopoietic Stem Cell Transplantation: Systematic Review and Meta-Analysis

Pia Raanani, Anat Gafter-Gvili, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, and Ofer Shpilberg

- Thirty trials including 4223 patients undergoing bone marrow transplantation (BMT) were included. **There was no difference in all-cause mortality when polyvalent IVIG or CMV-IVIG was compared to control**

- **there is no advantage in terms of survival or infection prevention, IVIG does not have a role in HSCT.**

Leukemia (2018) 32:1542–1560
https://doi.org/10.1038/s41375-018-0040-1

REVIEW ARTICLE

Multiple myeloma, gammopathies

Prevention and management of adverse events of novel agents in multiple myeloma: a consensus of the European Myeloma Network

Heinz Ludwig[1] · Michel Delforge[2] · Thierry Facon[3] · Hermann Einsele[4] · Francesca Gay[5] · Philippe Moreau[6] · Hervé Avet-Loiseau[7] · Mario Boccadoro[8] · Roman Hajek[9] · Mohamad Mohty[10] · Michele Cavo[11] · Meletios A Dimopoulos[12] · Jesús F San-Miguel[13] · Evangelos Terpos[12] · Sonja Zweegman[14] · Laurent Garderet[10] · María-Victoria Mateos[15] · Gordon Cook[16] · Xavier Leleu[17] · Hartmut Goldschmidt[18] · Graham Jackson[19] · Martin Kaiser[20] · Katja Weisel[21] · Niels W. C. J. van de Donk[14] · Anders Waage[22] · Meral Beksac[23] · Ulf H. Mellqvist[24] · Monika Engelhardt[25] · Jo Caers[26] · Christoph Driessen[27] · Joan Bladé[28] · Pieter Sonneveld[29]

Table 4 Recommendations on antimicrobial prophylaxis in multiple myeloma patients (adapted from NCCN Guidelines "Prevention and Treatment of Cancer-Related Infections" Version 1.2017 [7])

Risk factor	Microbial infection type	Prophylaxis recommendation	Details
Multiple myeloma diagnosis[a] Autologous or allogeneic[b] HSCT, Proteasome inhibitors	Viral	Consider prophylaxis during neutropenia and for sometime thereafter depending on risk	HSV or VZV infection or reactivation: acyclovir, famcyclovir, valaciclovir; Consider VZV prophylaxis after autologous HSCT Proteasome inhibitor therapy: VZV prophylaxis during active therapy including periods of neutropenia; CMV: prophylaxis in selected cases with repeated reactivation valgancyclovir or ganciclovir; in case of resistance or intolerance: foscarnet or cidofovir
	Bacterial	Consider prophylaxis	Trimethoprim–sulfamethoxazole, amoxicillin, quinolone
	Parasites	Consider prophylaxis	Trimethorpim–sulfamethoxazole, pentamidine-inhalation in allogeneic transplantation
	Fungal	Consider prophylaxis during neutropenia; consider pneumocystis pneumonia prophylaxis	Fluconazole[c] or micafungin[d]

NCCN Guidelines® Insights

Multiple Myeloma, Version 3.2018

Featured Updates to the NCCN Guidelines

Shaji K. Kumar, MD[1,*]; Natalie S. Callander, MD[2,*]; Melissa Alsina, MD[3]; Djordje Atanackovic, MD[4]; J. Sybil Biermann, MD[5]; Jorge Castillo, MD[6]; Jason C. Chandler, MD[7]; Caitlin Costello, MD[8,*]; Matthew Faiman, MD[9]; Henry C. Fung, MD[10]; Kelly Godby, MD[11]; Craig Hofmeister, MD, MPH[12,*]; Leona Holmberg, MD, PhD[13]; Sarah Holstein, MD, PhD[14]; Carol Ann Huff, MD[15]; Yubin Kang, MD[16]; Adetola Kassim, MD, MS[17,*]; Michaela Liedtke, MD[18,*]; Ehsan Malek, MD[9]; Thomas Martin, MD[19,*]; Vishala T. Neppalli, MD[20]; James Omel, MD[21,*]; Noopur Raje, MD[22]; Seema Singhal, MD[23]; George Somlo, MD[24]; Keith Stockerl-Goldstein, MD[25]; Donna Weber, MD[26]; Joachim Yahalom, MD[27]; Rashmi Kumar, PhD[28,*]; and Dorothy A. Shead, MS[28,*]

Prevista solo profilassi per HZV nei pazienti trattati con inibitori proteosoma e daratumumab

Profilassi anti Pneumocistis jirovecii in pazienti in terapia cronica con steroidi equivalenti alla dose di prednisone di 20 mg per un periodi di 4 settimane

Profilassi in HBV ad alto rischio

Conclusioni (1)

Il Mieloma si caratterizza per un elevato rischio di infezioni sia batteriche che virali

- Poche evidenze solide per la profilassi antibatterica di routine
- La profilassi anti Pneumocistis Jirovecii è consigliata nei pazienti per la terapia steroidea
- La profilassi antivirale (anti VZV) è obbligatoria in corso di terapia con (***IP, IMIDs, MoAb***)
- Warning sul CMV (possibili riattivazioni in corso PIs)

Conclusioni (2)

- La profilassi anti epatite B è fortemente consigliata nei pazienti con pregressa esposizione HBV- con Lamivudina (***IP, IMIDs, MoAb***)

- Non sono disponibili dati sul comportamento da tenere ' epatite C ma: «it seems reasonable to screen the high risk group (anti-HCV and/or HCV RNA) and to treat those with evidence of active infection with modern direct-acting antivirals «

- La terapia con Ig endovena non appare sostenuta da evidenze . Non esistono segnalazioni del loro uso con i nuovi farmaci . Utilizzo non standardizzato


THE END

Infections in Patients with Multiple Myeloma in the Era of High-Dose Therapy and Novel Agents

Marcio Nucci[1] and Elias Anaissie[2]

[1]University Hospital, Universidade Federal do Rio de Janeiro, Brazil; and [2]University of Arkansas for Medical Sciences, Little Rock, Arkansas

Profilassi con che cosa e a quali dosaggi?

Disease	Prophylaxis	Treatment
Bacterial infection		
Neutropenic	FQ[a,b]	Antipseudomonal β-lactam antibiotic[b,c]
Nonneutropenic	TMP-SMX 800 mg/160 mg orally daily [102] or daily FQ[d]	Broad spectrum antibiotic (FQ,[a] β-lactam, other)[d]; if FQ not used in prophylaxis, add a FQ[a] or macrolide[e] for pneumonia[d]
CDAD	Consider metronidazole prophylaxis (500 mg orally 3× daily) if prior history of CDAD[f]	Metronidazole 500 mg orally 3× daily or vancomycin– 125 mg orally 4× daily[b]; treat for 2–4 weeks [103]
Tuberculosis	Isoniazid 300 mg orally daily[f] [104]	Various regimens [105]
Fungal infection		
Oral and/or esophageal candidiasis	Clotrimazole troches (10 mg 5× per day) or fluconazole 100–200 mg orally daily[b] [106]	Fluconazole 200–400 mg orally daily for 7–10 days[b] [106]
Pneumocystis jirovecii pneumonia	TMP-SMX 800 mg/160 mg orally daily or twice/week,[b] pentamidine 300 mg aerosol monthly,[b] dapsone 100 mg orally daily,[d] atovaquone 1500 mg orally daily[d] [19]	TMP-SMX 15–20 mg/kg of TMP IV daily[d] or pentamidine– 4 mg/kg IV daily[d] [19]; treat for 3 weeks and give secondary prophylaxis
Viral infection		
Herpes simplex virus	Acyclovir 200– 400 mg twice or 3× daily,[b] valacyclovir 500 mg orally 3× daily,[b] or famciclovir 500 mg orally 3× daily[b] [107]	7–14 days of acyclovir 250 mg/m² IV 3× daily,[b] valacyclovir 1 g orally 3× daily,[b] or famciclovir 500 mg orally twice daily[b] [107]
Herpes zoster virus	Acyclovir 400 mg orally twice or 3× daily,[b] valacyclovir 500 mg orally 3× daily,[b] or famciclovir 500 mg orally 3× daily[b] [107]	7–14 days of acyclovir 500 mg/m² IV 3× daily,[b] valacyclovir 1 g orally 3× daily,[b] or famciclovir 500 mg orally twice daily[b] [107]
Cytomegalovirus	Ganciclovir 5 mg/kg IV twice daily,[b] or valganciclovir 900 mg/day orally,[b] or foscarnet 60 mg/kg IV twice daily[b] [107]	14–21 days of ganciclovir IV- 5 mg/kg IV twice daily, or valganciclovir 900 mg/day orally twice daily, or foscarnet 90 mg/kg IV twice daily [107]
Influenza virus	Oseltamivir 75 mg orally daily for the duration of the Influenza season [107] (resistance of influenza A H1N1 subtype is increasingly reported [108])[g]	Oseltamivir 75 mg orally twice daily for 5–7 days [107]

Terapia antibiotica profilattica e nuovi farmaci??

Dalle linee guida europeee….

prophylaxis with either trimethoprim–sulfamethoxazole, amoxicillin, or a quinolone should be considered for the first months after start of therapy in selected patients with high risk for bacterial infections such as very elderly patients, those with a history of several previous infections, and those exposed to regimes with a high risk of infectious complications.

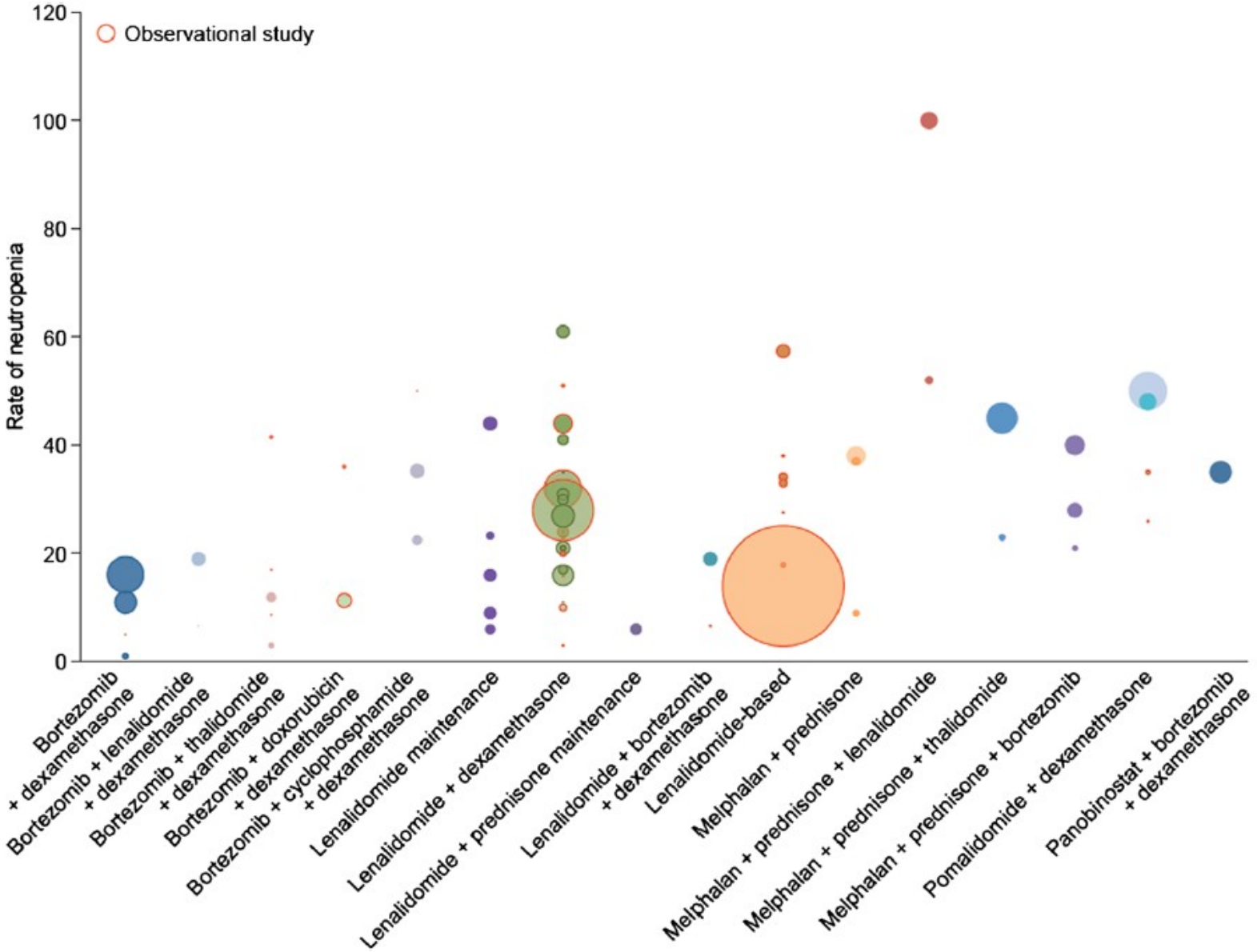

Observational study
Rate of neutropenia
120
100
80
60
40
20
0
Bortezomib + dexamethasone
Bortezomib + lenalidomide + dexamethasone
Bortezomib + thalidomide + dexamethasone
Bortezomib + doxorubicin + dexamethasone
Bortezomib + cyclophosphamide + dexamethasone
Lenalidomide maintenance
Lenalidomide + dexamethasone
Lenalidomide + prednisone maintenance
Lenalidomide + bortezomib + dexamethasone
Lenalidomide-based
Melphalan + prednisone
Melphalan + prednisone + lenalidomide
Melphalan + prednisone + thalidomide
Melphalan + prednisone + bortezomib
Pomalidomide + dexamethasone
Panobinostat + bortezomib + dexamethasone

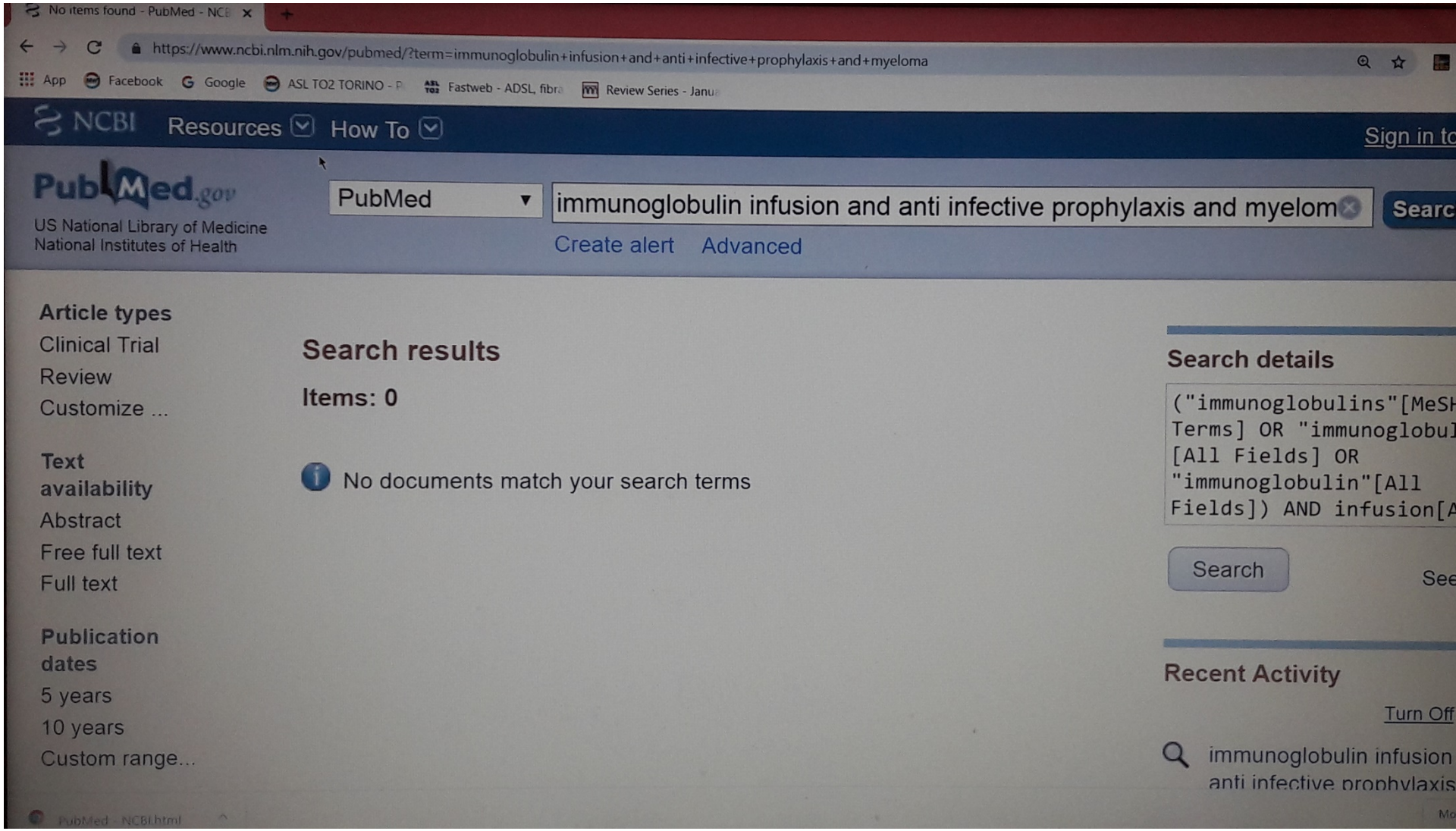
Table 1 Neutropenia rates by regimen

Regimen	Range of reported grade 3 and 4 neutropenia, %	Numb of stud
Thalidomide	0–≤5	1
CTD	0–≤5	1
VT	0–≤5	1
VP	0–≤5	1
Bortezomib	0–≤5	2
	>5–≤10	1
	>10–≤25	7
	>25–≤50	0
VD	0–≤5	2
	>5–≤10	1
	>10–≤25	2
VTD	0–≤5	2
	>10–≤25	2
	>25–≤50	1
Bortezomib-based	>5–≤10	1
	>10–≤25	2

Table 1 Neutropenia rates by regimen

Regimen	Range of reported grade 3 and 4 neutropenia, %	Number of studies
Lenalidomide maintenance	>5–≤10	2
	>10–≤25	2
	>25–≤50	1
RD	0–≤5	1
	>5–≤10	1
	>10–≤25	11
	>25–≤50	9
	>50–≤75	2
RP maintenance	>5–≤10	1
RVD	>5–≤10	1
	>10–≤25	1
Lenalidomide-based	>10–≤25	2
	>25–≤50	5
ERD	>25–≤50	1
MP	>5–≤10	1
	>25–≤50	2
MPT	>10–≤25	1
	>25–≤50	1
PAN-BTZ-Dex	>25–≤50	1
VCD	>10–≤25	1
	>25–≤50	2
VMP	>10–≤25	1
	>25–≤50	2
VMPT	>25–≤50	1
PAD	>10–≤25	2
RCD consolidation	>10–≤25	1
PD	>25–≤50	4
PVD	>25–≤50	1

Regimen	Range of reported grade 3 and 4 neutropenia, %	Number of studies
IRD	> 10–≤ 25	1
Vorinostat + bortezomib	> 10–≤ 25	1
KRD	> 25–≤ 50	1
MPR	> 50–≤ 75	1
	> 75–100	1
CHOP	> 50–≤ 75	1
HD-M	> 50–≤ 75	1
	> 75–100	3
VTD-PACE	> 50–≤ 75	1
	> 75–100	1
PACE	> 75–100	1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European Myeloma Network Guidelines for the Management of Multiple Myeloma-related Complications

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GUIDELINE ARTICLE

Table 2. Incidence of adverse events in multiple myeloma patients treated with different therapy regimens.

Regimens	Neutropenia (%)	VTE (%)	PN (%)	Infection (%)	SPM (%)
Induction					
MPT	16-48	3-12	6-23	4-28	NA
CTD	NA	16	7	13	NA
VMP	40	1	22	10	6
VMPT	38	5	15	13	NA
VTP	22	2	9	1	NA
VRd	9	5	6	5	NA
Rd	20	12	2	9	NA
MPR	66	5	0	13	2
Salvage					
V	14	0	8	13	NA
RD	41	15	2	22	NA

CTD: cyclophosphamide-thalidomide-dexamethasone; MPR: melphalan-prednisone-lenalidomide; NA: not available, Rd: lenalidomide plus low-dose dexamethasone; RD: lenalidomide plus high-dose dexamethasone; SPM: second primary malignancy; V: bortezomib; VMP: bortezomib-melphalan-thalidomide; VMPT: bortezomib-melphalan-prednisone-thalidomide; VTE: venous thromboembolism; VTP: bortezomib-melphalan-prednisone (adapted according Palumbo et al.[100]).