Policitemia vera: la terapia convenzionale

Quinta
Giornata Fiorentina
dedicata ai pazienti con
malattie mieloproliferative
croniche

Sabato 9 Maggio 2015

laboratorio congiunto sulle
malattie mieloproliferative croniche

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Istituto di Ematologia
Università Cattolica
Policlinico Agostino Gemelli
Roma

TROMBOSI – POLICITEMIA VERA

			% (diagnosi)		% (follow-up)	
		N	Arteriose	Venose	Arteriose	Venose
Anger et al, 1989	PV	141	18		40	
Wehmeier et al, 1991	PV	84	18		18	
GISP, 1995	PV	1213	22	12	8	6
Passamonti et al, 2002	PV	163	22	12	15	3
Passamonti et al, 2004	PV	396	29		7	4
Marchioli et al, 2006	PV	1638	29	14	5	5
Barbui et al, 2014	PV	1545	16	7	12	9

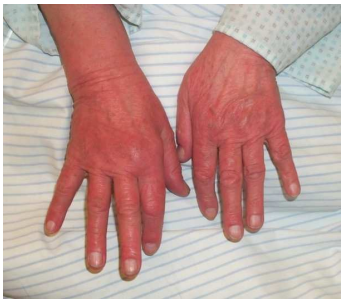
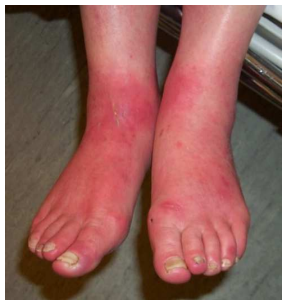
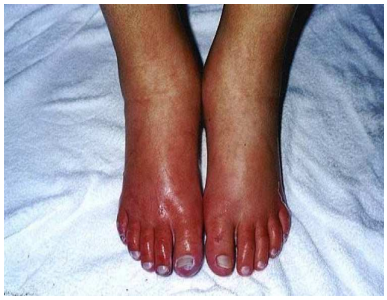
Modificato da Elliott & Tefferi, Br J Haematol 2004

TROMBOSI – TROMBOCITEMIA ESSENZIALE

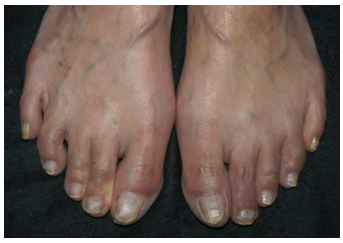
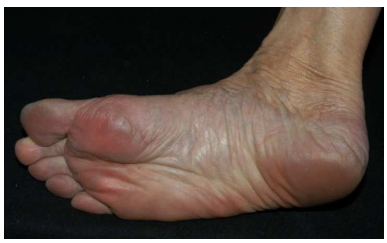
			% (diagnosi)		% (follow-up)	
		N	Arteriose	Venose	Arteriose	Venose
Bellucci et al, 1986	ET	94	18	4	11	6
Fenaux et al, 1990	ET	147	15	3	12	2
Cortelazzo et al, 1990	ET	100	10	1	14	6
Colombi et al, 1991	ET	103	20	3	10	1
Besses et al, 1999	ET	148	25		21	1
Jensen et al, 2000	ET	96	12	2	11	6
Passamonti et al, 2004	ET	435	19		8	7
Chim et al, 2005	ET	231	12	0	9	1
Gangat et al, 2014	ET	300	12	7	17	8

Modificato da Elliott & Tefferi, Br J Haematol 2004

Eritromelalgia

Acrocianosi

INCIDENZA ANNUALE DI TROMBOSI IN COORTI DI PAZIENTI CON POLICITEMIA VERA

	N	Disegno	Citoriduzione (%)	Antiaggreganti (%)	Trombosi (% pz.-anno)
GISP, 1995	1213	Retrosp.	69	Non disponibile	3.2
Passamonti et al, 2004	396	Retrosp.	86	57	1.1
Marchioli et al, 2005	1638	Prospet.	62	58	4.9
De Stefano et al, 2008	235	Retrosp.	66	71	6.0 (ricorrenze)
Marchioli et al, 2013	365	Prospett.	60	84	1.9 (Htc <45%) 5.0 (Htc 45-50%)
Barbui et al, 2014	1545	Retrosp.	73	84	1.6 arteriosa 1.0 venosa

Modificato da Patrono, Rocca & De Stefano, Blood 2013

INCIDENZA ANNUALE DI TROMBOSI IN COORTI DI PAZIENTI CON TROMBOCITEMIA ESSENZIALE

	N	Disegno	Citoriduzione (%)	Antiaggreganti (%)	Trombosi (% pz.-anno)
Cortelazzo et al, 1990	100	Retrosp.	74	1	6.6
Colombi et al, 1991	103	Retrosp.	65	72	2.2
De Stefano et al, 2008	259	Retrosp.	75	75	5.2 (ricorrenze)
Carobbio et al, 2008	1063	Retrosp.	51	66	2.3
Harrison et al, 2008	809	Prospet.	72	100	2.6
Passamonti et al, 2008	605	Retrosp.	67	33	1.3
Carobbio et al, 2011	891	Retrosp.	57	68	1.8
Gisslinger et al, 2013	730	Prospect.	63	28	3.1

Modificato da Patrono, Rocca & De Stefano, Blood 2013

VOLUME 23 · NUMBER 10 · APRIL 1 2005
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Vascular and Neoplastic Risk in a Large Cohort of Patients With Polycythemia Vera

Roberto Marchioli, Guido Finazzi, Raffaele Landolfi, Jack Kutti, Heinz Gisslinger, Carlo Patrono, Raphael Marilus, Ana Villegas, Gianni Tognoni, and Tiziano Barbui

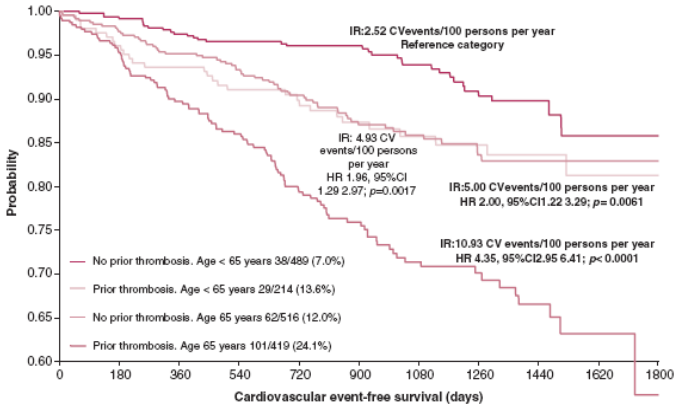


Figure 1. Incidence of thrombotic events by risk factors in the ECLAP study.[2]

Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera

Raffaele Landolfi,[1,2] Leonardo Di Gennaro,[1] Tiziano Barbui,[3] Valerio De Stefano,[1] Guido Finazzi,[3] RosaMaria Marfisi,[4] Gianni Tognoni,[4] and Roberto Marchioli,[4] for the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP)

[1]Catholic University School of Medicine, Rome, Italy; [2]Instituto di Ricovero e Cura e Carattera Scientifico Oasi Maria Santissima, Troina, Italy; [3]Ospedali Riuniti, Bergamo, Italy; [4]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy

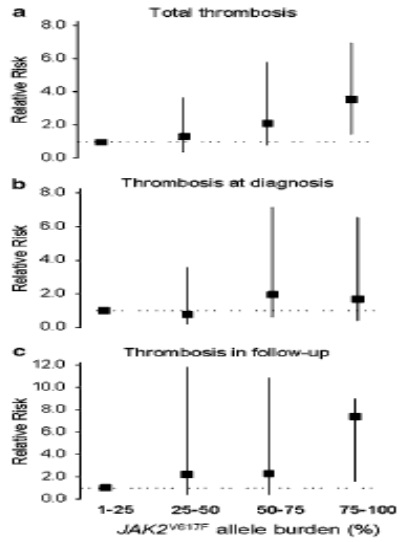
Nella coorte ECLAP (1638 pazienti con PV) il rischio di eventi trombotici maggiori era aumentato nei pazienti con leucociti > 15,000 x 10^6 / L rispetto ai pazienti con leucociti < 10,000 x 10^6 / L (hazard ratio 1.7, CI 1.1-2.6)

Il rischio era 2.8 (CI 1.2-6.5) per l'infarto del miocardio, 0.9 (CI 0.4-2.3) per ischemia cerebrale, e 1.8 (CI 0.8-3.9) per tromboembolismo venoso

Blood, 2007

Prospective identification of high-risk polycythemia vera patients based on *JAK2*^{V617F} allele burden

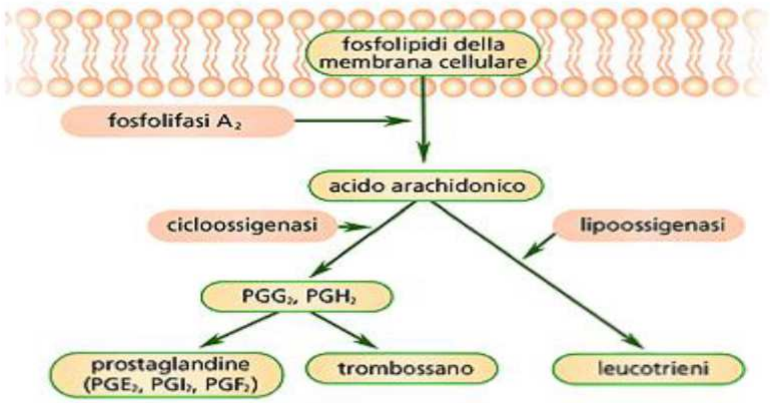
AM Vannucchi[1], E Antonioli[1], P Guglielmelli[1], G Longo[1], A Pancrazzi[1], V Ponziani[1], C Bogani[1], P Rossi Ferrini[1], A Rambaldi[2], V Guerini[2], A Bosi[1] and T Barbui[2], for the MPD Research Consortium[3]



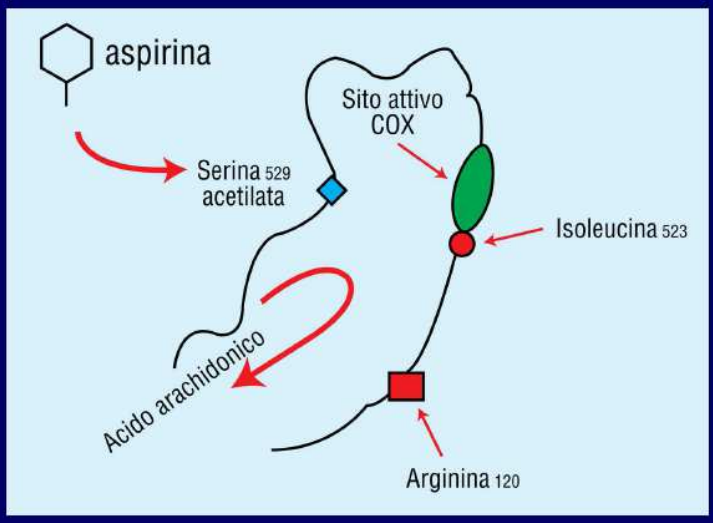
Leukemia, 2007

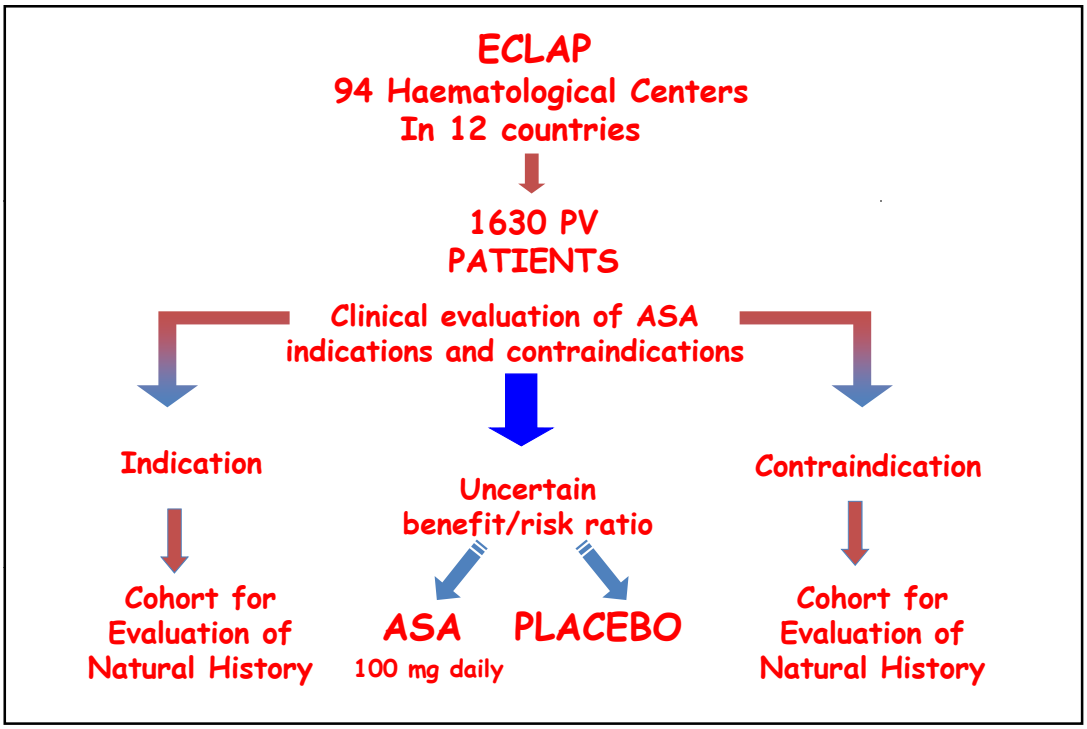
Profilassi antitrombotica

Meccanismo d'azione dei FANS



Meccanismo di azione dell'aspirina: Inibizione irreversibile COX-1

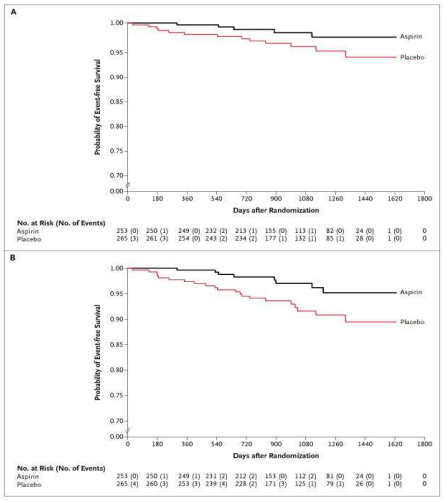




Baseline Characteristics

(%)	ASA	Placebo
Prior thrombosis	11.1	9.4
Prior arterial thrombosis	5.1	4.5
AMI	0.8	1.5
Stroke	1.6	0.8
TIA	0.8	1.5
Peripheral	2.0	0.8
Pulmonary embolism	0.8	0.4
Prior venous thrombosis	7.5	5.7
Deep vein thrombosis	4.0	1.5
Superficial thrombosis	4.0	4.2

Probability of Survival Free of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes (Panel A) and Probability of Survival Free of Myocardial Infarction, Stroke, Death from Cardiovascular Causes, Pulmonary Embolism, and Deep Venous Thrombosis (Panel B)



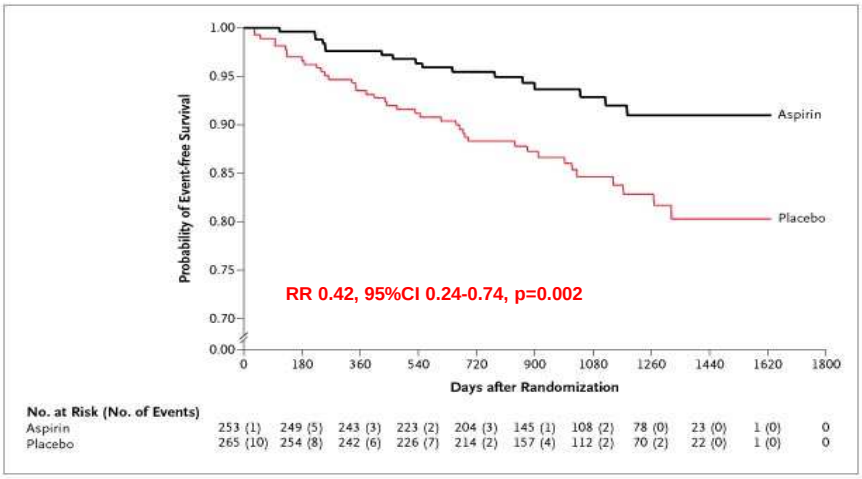
RR 0.41, 95%CI 0.15-1.15, p=0.08

RR 0.40, 95%CI 0.18-0.91, p=0.02

Landolfi, R. et al. N Engl J Med 2004;350:114-124

The NEW ENGLAND JOURNAL of MEDICINE

Probability of Survival Free of a Thrombotic Event



Landolfi, R. et al. N Engl J Med 2004;350:114-124

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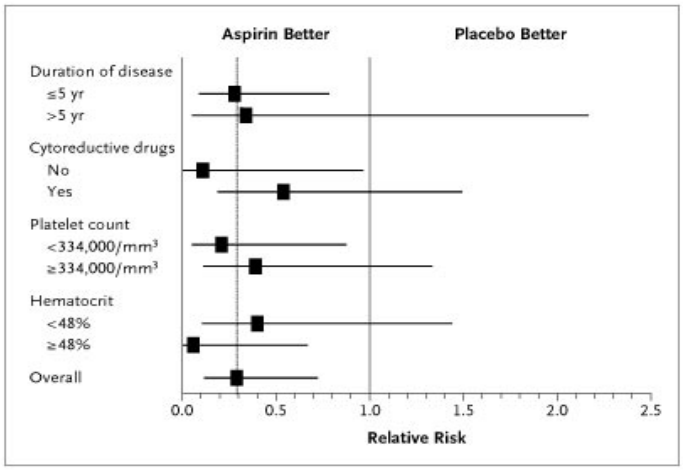
Effect of Aspirin on the Risk of a Major Arterial or Venous Event or Death from Cardiovascular Causes in Various Subgroups



Landolfi, R. et al. N Engl J Med 2004;350:114-124

Rates and Relative Risks of Bleeding Episodes in the Two Groups

Table 3. Rates and Relative Risks of Bleeding Episodes in the Two Groups.*

Type of Bleeding Episode	Aspirin Group (N=253)	Placebo Group (N=265)	Relative Risk (95% CI)	P Value
	no. (%)			
Any bleeding	23 (9.1)	14 (5.3)	1.82 (0.94–3.53)	0.08
Major bleeding	3 (1.2)	2 (0.8)	1.62 (0.27–9.71)	0.60
Gastrointestinal	2 (0.8)	0		
Intracranial	1 (0.4)	2 (0.8)		
Minor bleeding	20 (7.9)	12 (4.5)	1.83 (0.90–3.75)	0.10
Hematoma	2 (0.8)	2 (0.8)		
Gastrointestinal	7 (2.8)	3 (1.1)		
Hematuria	1 (0.4)	3 (1.1)		
Epistaxis	9 (3.6)	1 (0.4)		
Other	2 (0.8)	4 (1.5)		

* Major bleeding was defined as any bleeding episode that was fatal or necessitated transfusions or hospitalization. Totals for categories may not equal the sum of the values for subcategories because some patients had more than one type of bleeding episode. CI denotes confidence interval.

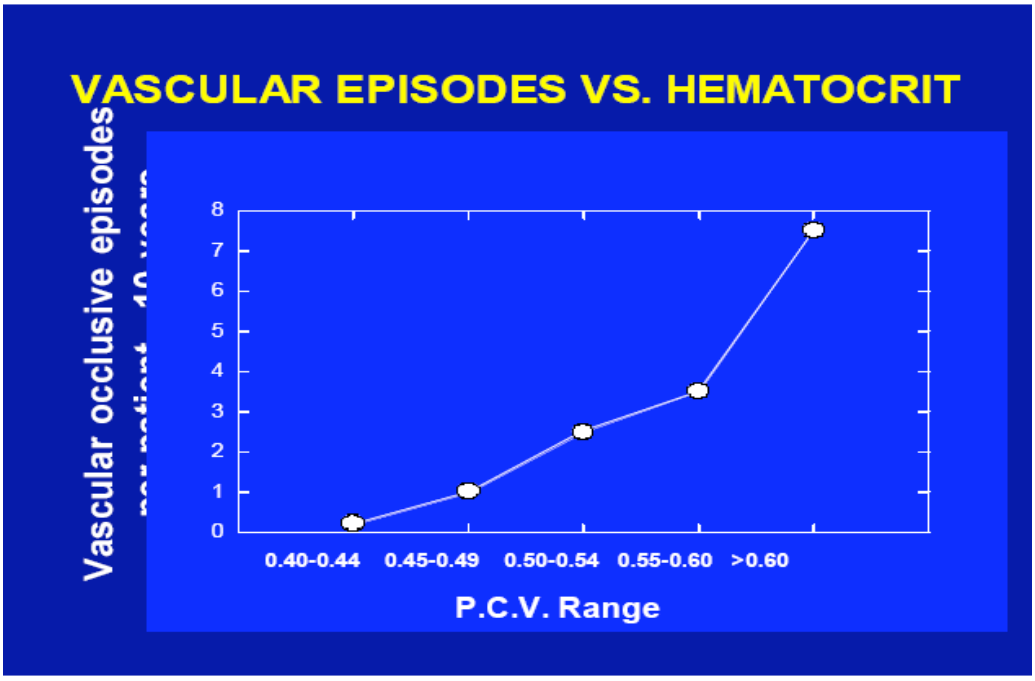
Landolfi, R. et al. N Engl J Med 2004;350:114-124

CITORIDUZIONE

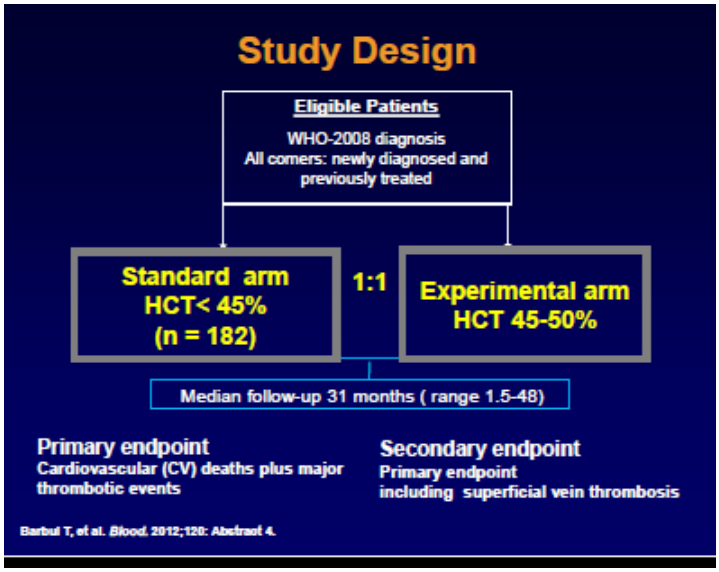
- Salasso terapeutico

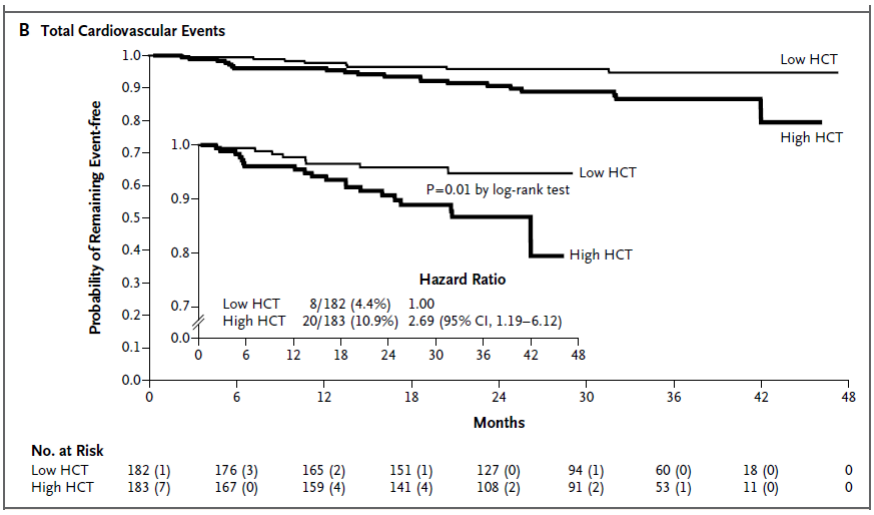
- Idrossiurea
- Pipobromano (Vercite)
- Busulfano (Myleran)

- Anagrelide
- Interferone



STUDIO CYTO-PV





Marchioli et al, NEJM 2013

HYDROXYUREA FOR PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA AND A HIGH RISK OF THROMBOSIS

SERGIO CORTELAZZO, M.D., GUIDO FINAZZI, M.D., MARCO RUGGERI, M.D., OSCAR VESTRI, M.D., MONICA GALLI, M.D., FRANCESCO RODEGHIERO, M.D., AND TIZIANO BARBUI, M.D.

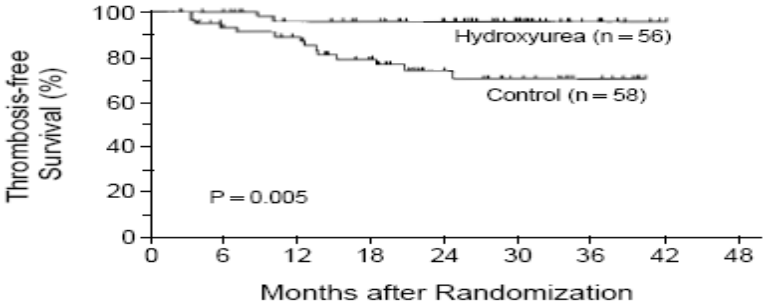


Figure 2. Probability of Thrombosis-free Survival in 114 Patients with Essential Thrombocythemia Treated with Hydroxyurea or Left Untreated.

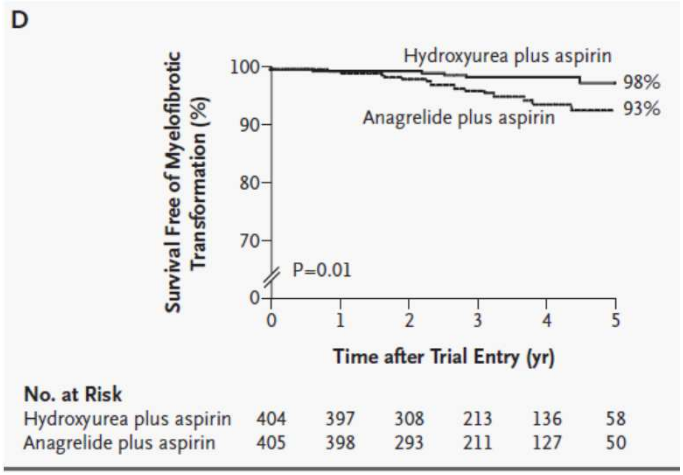
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

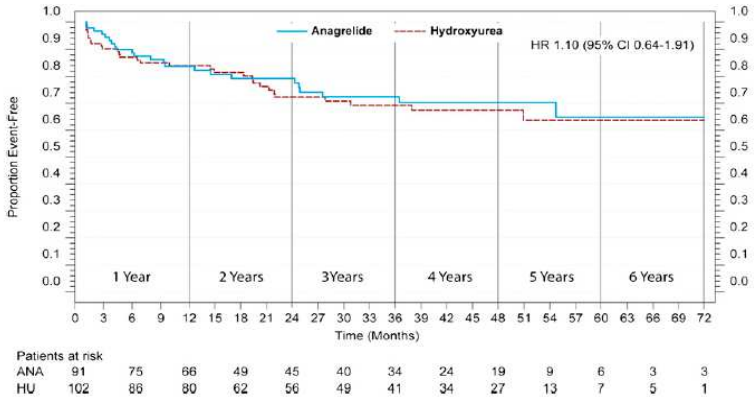
Hydroxyurea Compared with Anagrelide in High-Risk Essential Thrombocythemia

Claire N. Harrison, M.R.C.P., M.R.C.Path., Peter J. Campbell, F.R.A.C.P., F.R.C.P.A., Georgina Buck, M.Sc., Keith Wheatley, D.Phil., Clare L. East, B.Sc., David Bareford, M.D., F.R.C.P., Bridget S. Wilkins, M.D., F.R.C.Path., Jon D. van der Walt, M.D., F.R.C.Path., John T. Reilly, F.R.C.P., F.R.C.Path., Andrew P. Grigg, F.R.A.C.P., F.R.C.P.A., Paul Revell, M.D., F.R.C.P., Barrie E. Woodcock, F.R.C.P., F.R.C.Path., and Anthony R. Green, F.R.C.Path., F.Med.Sci., for the United Kingdom Medical Research Council Primary Thrombocythemia 1 Study*

2005



Harrison et al, PT-1 trial, NEJM 2005



Gisslinger et al, ANAHYDRET Study, Blood 2013

Original Article

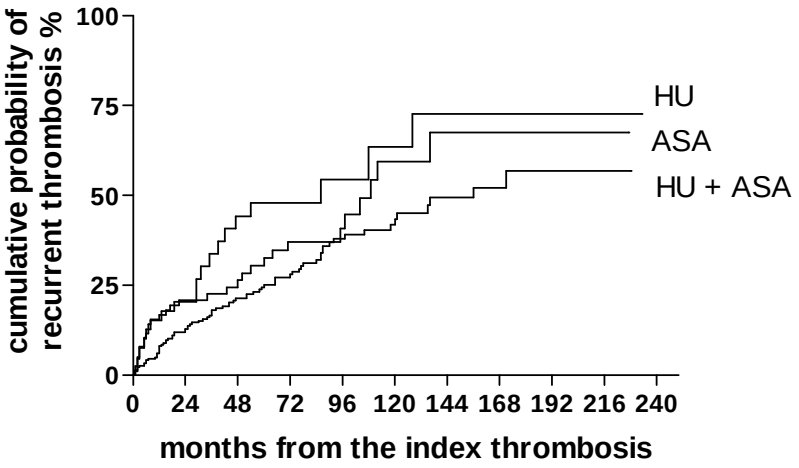
Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments

Valerio De Stefano,[1] Tommaso Za,[1] Elena Rossi,[1] Alessandro M. Vannucchi,[2] Marco Ruggeri,[3] Elena Elli,[4] Caterina Micò,[5] Alessia Tieghi,[6] Rossella R. Cacciola,[7] Cristina Santoro,[8] Giancarla Gerli,[9] Nicola Vianelli,[10] Paola Guglielmelli,[2] Lisa Pieri,[2] Francesca Scognamiglio,[3] Francesco Rodeghiero,[3] Enrico M. Pogliani,[4] Guido Finazzi,[5] Luigi Gugliotta,[6] Roberto Marchioli,[11] Giuseppe Leone,[1] and Tiziano Barbui[5] *for the GIMEMA CMD-Working Party*

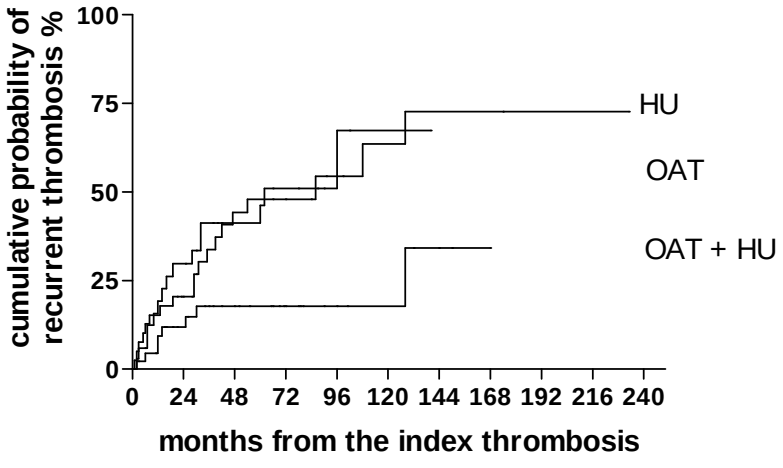
[1]Institute of Hematology, Catholic University, Rome; [2]Dept. of Hematology, University of Florence, Florence; [3]Hematology Department and Hemophilia and Thrombosis Center, San Bortolo Hospital, Vicenza; [4]Hematology Division and Bone Marrow Transplantation Unit, San Gerardo Hospital, University of Milano-Bicocca, Monza; [5]Dept. of Hematology-Oncology, Ospedali Riuniti, Bergamo; [6]Hematology Unit, Santa Maria Nuova Hospital, Reggio Emilia; [7]the Dept. of Biomedical Sciences, Section of Hematology, University of Catania, Catania; [8]Institute of Hematology, Dept. of Cellular Biotechnology and Hematology, University La Sapienza, Rome; [9]Hematology and Thrombosis Unit, San Paolo Hospital, University of Milan, Milan; [10]Institute of Hematology and Oncology L. and A. Seràgnoli, University of Bologna, Bologna; [11]Laboratory of Epidemiology of Cardiovascular Disease, Dept. of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy

Efficacia del trattamento sul rischio di ricorrenza trombotica in pazienti con PV o TE e un primo evento trombotico arterioso o venoso (analisi multivariata)

	Primo evento arterioso (n= 341)		**Primo evento venoso (n= 160)**	
	Rischio relativo (95% IC)	**P**	**Rischio relativo (95% CI)**	**P**
Antiaggreganti	**0.67 (0.41-1.08)**	**0.10**	***0.42 (0.22-0.77)***	***0.006***
Anticoagulanti orali	**1.01 (0.93-1.09)**	**0.73**	***0.32 (0.15-0.64)***	***0.001***
Salasso	**0.76 (0.43-1.31)**	**0.33**	**0.72 (0.35-1.47)**	**0.38**
Citoriduzione	***0.47 (0.31-0.70)***	***0.0003***	**0.66 (0.38-1.13)**	**0.14**



HU + ASA vs HU: hazard ratio 0.56 (95% CI 0.24 – 0.85)
HU + ASA vs ASA: hazard ratio 0.67 (95% CI 0.41 – 0.99)



HU + OAT vs HU: hazard ratio 0.37 (95% CI 0.17 – 0.79)
HU + OAT vs OAT: hazard ratio 0.33 (95% CI 0.13 – 0.74)

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations From European LeukemiaNet

Tiziano Barbui, Giovanni Barosi, Gunnar Birgegard, Francisco Cervantes, Guido Finazzi, Martin Griesshammer, Claire Harrison, Hans Carl Hasselbalch, Rudiger Hehlmann, Ronald Hoffman, Jean-Jacques Kiladjian, Nicolaus Kröger, Ruben Mesa, Mary F. McMullin, Animesh Pardanani, Francesco Passamonti, Alessandro M. Vannucchi, Andreas Reiter, Richard T. Silver, Srdan Verstovsek, and Ayalew Tefferi

From the Ospedali Riuniti di Bergamo, Bergamo; Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo Foundation; University of Pavia, Pavia; Università degli Studi, Firenze, Italy; Uppsala University, Uppsala, Sweden; Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; Johannes Wesling Medical Centre Minden, Academic Hospital of the University of Hannover, Minden; III Medizinische Universitätsklinik, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim; University Hospital Hamburg-Eppendorf, Hamburg, Germany; Guy's and St Thomas' National Health Service Foundation Trust, London; Centre for Cancer Research and Cell Biology, Queen's University, Belfast, United Kingdom; Roskilde Hospital, University of Copenhagen, Copenhagen, Denmark; Tisch Cancer Institute, Mount Sinai School of Medicine; Weill Medical College of Cornell University, New York, NY; Mayo Clinic, Scottsdale, AZ; Mayo Clinic, Rochester, MN; The University of Texas MD Anderson Cancer Center, Houston, TX; and Assistance Publique–Hôpitaux de Paris, Hôpital Saint-Louis, Université Paris 7, Paris, France.

A B S T R A C T

We present a review of critical concepts and produce recommendations on the management of Philadelphia-negative classical myeloproliferative neoplasms, including monitoring, response definition, first- and second-line therapy, and therapy for special issues. Key questions were selected according the criterion of clinical relevance. Statements were produced using a Delphi process, and two consensus conferences involving a panel of 21 experts appointed by the European LeukemiaNet (ELN) were convened. Patients with polycythemia vera (PV) and essential thrombocythemia (ET) should be defined as high risk if age is greater than 60 years or there is a history of previous thrombosis. Risk stratification in primary myelofibrosis (PMF) should start with the International Prognostic Scoring System (IPSS) for newly diagnosed patients and dynamic IPSS for patients being seen during their disease course, with the addition of cytogenetics evaluation and transfusion status. High-risk patients with PV should be managed with phlebotomy, low-dose aspirin, and cytoreduction, with either hydroxyurea or interferon at any age. High-risk patients with ET should be managed with cytoreduction, using hydroxyurea at any age. Monitoring response in PV and ET should use the ELN clinicohematologic criteria. Corticosteroids, androgens, erythropoiesis-stimulating agents, and immunomodulators are recommended to treat anemia of PMF, whereas hydroxyurea is the first-line treatment of PMF-associated splenomegaly. Indications for splenectomy include symptomatic portal hypertension, drug-refractory painful splenomegaly, and frequent RBC transfusions. The risk of allogeneic stem-cell transplantation–related complications is justified in transplantation-eligible patients whose median survival time is expected to be less than 5 years.

J Clin Oncol 28. © 2011 by American Society of Clinical Oncology

Raccomandazioni European LeukemiaNet (JCO 2011)

- PV (prima linea)

  Salassoterapia (per ottenere Htc <45%)

  ASA 100 mg / die

  Citoriduzione (HU) in pazienti non responsivi ai salassi o ad alto rischio

  Cautela nella prescrizione di HU in pazienti < 40 anni

- PV (seconda linea)

  Interferone

ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES
AJH Educational Material

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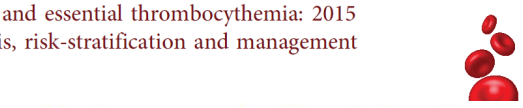
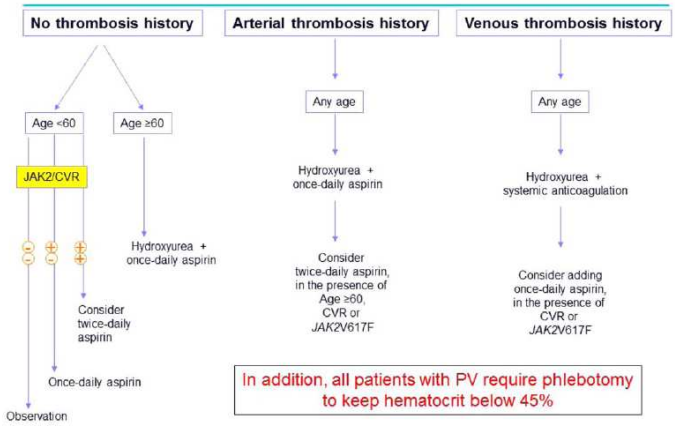
Polycythemia vera and essential thrombocythemia: 2015 update on diagnosis, risk-stratification and management

Ayalew Tefferi[1]* and Tiziano Barbui[2]



Contemporary treatment algorithm in essential thrombocythemia and polycythemia vera



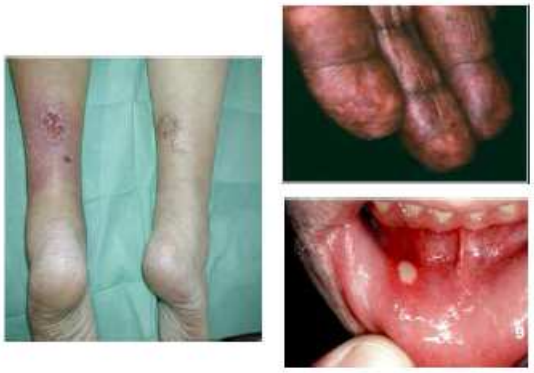
Categoria		Trattamento
Basso rischio	Età < 60 anni e anamnesi negativa per trombosi	Salassoterapia Correzione dei FRCV Aspirina
Alto rischio	Età > 60 anni e/o anamnesi positiva per trombosi	Citoriduzione Correzione dei FRCV Aspirina (Anti-vitamina K) +/- Salassoterapia

Vannucchi, How I treat PV, Blood 2014

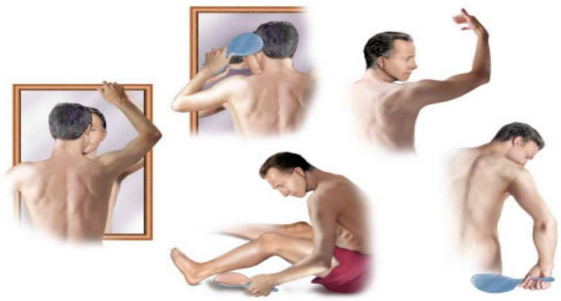
Per chi assume idrossiurea

- L'idrossiurea può indurre nel 5-10% dei casi complicanze di tipo dermatologico

  (afte, ulcere cutanee, cheratosi)



Eseguire un **autocontrollo periodico della cute** in maniera da poter riferire all'ematologo al momento della visita di controllo lesioni sospette.



Prevenzione complicanze dermatologiche

- Mantenere la pelle idratata
- Evitare l'eccessiva esposizione al sole (in caso impiegare creme schermanti)
- Usare calzature comode, evitando microtraumatismi in zona malleolare.

Seconda linea

- Interferone
- Pipobromano (Vercite ®)
- Busulfano (Myleran ®)
- Ruxolitinib (Jakavi ®) (approvazione FDA 4.12.2014)

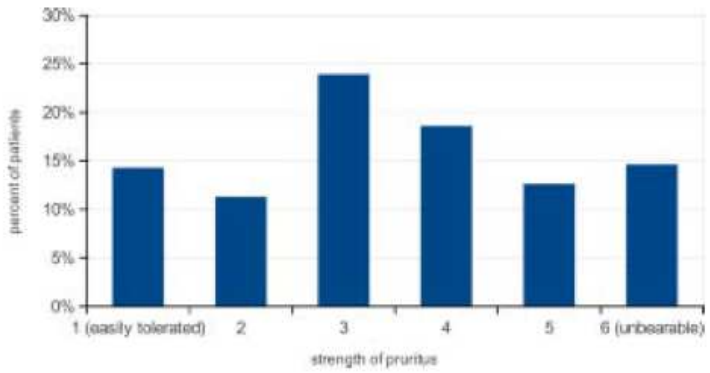


Figure 3. Subjective intensity of AP on a scale from 1 to 6.

Siegel et al, Am J Hematolol 2013 (441 PV patients)

TABLE VII. Treatment of AP

Drug	Total	No benefit	Mediocre benefit	Good benefit
Antihistaminics	39 (13.0%)	16 (41.0%)	11 (28.2%)	12 (30.8%)
GABA-Analogues	3 (1.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)
Benzodiazepines	2 (0.7%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
Tricyclic-antidepressants	1 (0.3%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
SSRIs	5 (1.7%)	3 (60.0%)	2 (40.0%)	0 (0.0%)
Steroids	4 (1.3%)	0 (0.0%)	0 (0.0%)	4 (100.0%)
Carbamazepine	1 (0.3%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Polidocanol	1 (0.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Cromoglicinic acid	1 (0.3%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Oil-Lotions	9 (3.0%)	1 (11.1%)	3 (33.3%)	5 (55.6%)
UV-Treatment	4 (1.3%)	1 (25.0%)	2 (50.0%)	1 (25.0%)
Crotamiton	1 (0.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Immunoglobulins	1 (0.3%)	0 (0.0%)	1 (100.0%)	0 (0.0%)

TABLE VIII. Response of AP to PV Therapy

	Resolved	Much better	Slightly better	Equal	Worse
Number of patients	17 (5.6%)	53 (17.6%)	46 (15.3%)	121 (40.2%)	31 (10.3%)

Numbers show total number of patients, in parentheses are percentages relative to total number of patients with AP.

TABLE IX. Response of AP to Different PV Treatment

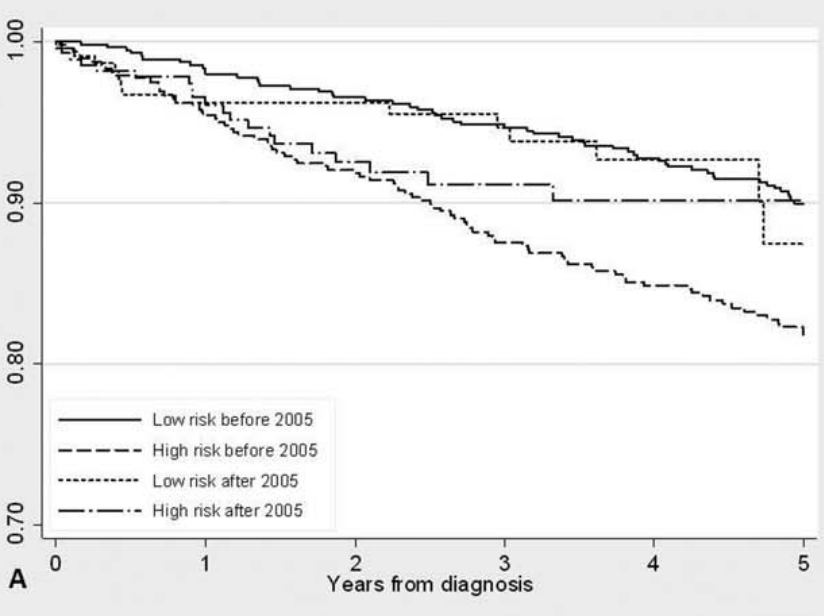
	Number of patients	Better	Equal	Worse
Hydroxyurea	101	43 (42.6%)	42 (41.6%)	16 (15.8%)
ASS	113	52 (46.0%)	54 (47.8%)	7 (6.2%)
Clopidogrel	9	4 (44.4%)	4 (44.4%)	1 (11.1%)
Anagrelide	7	3 (42.9%)	4 (57.1%)	0 (0.0%)
Coumadin	11	4 (36.4%)	5 (45.5%)	2 (18.2%)
Interferon-alpha	23	12 (52.2%)	6 (26.1%)	5 (21.7%)
Heparin	1	1 (100.0%)	0 (0.0%)	0 (0.0%)
Azathioprin	1	0 (0.0%)	1 (100.0%)	0 (0.0%)
P32	1	1 (100.0%)	0 (0.0%)	0 (0.0%)

PRURITO

- Il prurito è peggiorato dal contatto con l'acqua.
- Vanno evitati bagni o docce con acqua molto calda e per lavarsi va preferita l'acqua fredda, asciugandosi a pressione e non per strofinio.
- L'uso di indumenti stretti o di fibre sintetiche può peggiorare il prurito.

PRURITO - II

- La pelle va tenuta idratata, impiegando apposite creme o lozioni.
- È stato segnalato un beneficio con l'impiego di soluzioni di bicarbonato di sodio o di creme galeniche alla capsaicina (sostanza attiva del peperoncino).
- Può essere utile, per alcuni soggetti o in particolari situazioni, l'assunzione di farmaci antistaminici, anche se il loro impiego può essere limitato dall'eccessivo effetto sedativo generale.
- Trattamenti con raggi ultravioletti possono essere tentati con controllo specialistico dermatologico.



Barbui et al, Am J Hematol 2015 (1545 PV patients)