La Terapia della Piastrinopenia Immune (ITP)

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ITP: quando iniziare la terapia

• Il numero delle piastrine non deve essere l'unico parametro guida; è necessario considerare l'eventuale presenza ed entità della clinica emorragica, l'età del paziente, il suo stile di vita, la presenza di co-morbidità

• Necessario ponderare attentamente gli effetti collaterali dovuti al trattamento, a fronte di efficacia spesso poco prevedibile e transitoria

⇩

• piastrine < 20-30x10^9/L

• piastrine > 20-30x10^9/L e sindrome emorragica

Scopo della terapia: - proteggere dall'emorragia maggiore
- ottenere n° plt emostaticamente valido (>20-30x10^9/L)
- consentire di mantenere una buona qualità di vita

• <10% dei casi raggiunge entro 6-12 mesi la RC spontaneamente

RISCHIO EMORRAGICO
FATTORI CONDIZIONANTI

- **Età del paziente**
- **Entità della piastrinopenia**
- **Durata della piastrinopenia**
- **Presenza di locus minoris resistentiae**
- **Febbre**
- **Associazione di coagulopatia**
- **Presenza di co-morbidità (uremia, ipertensione arteriosa, diabete, integrità endotelio, ecc.)**
- **Uso di TAO/NAO o di farmaci che interferiscono con la funzione piastrinica**
- **Stile di vita**

Trattamento di I linea: raccomandazioni internazionali

Intervention	Initial response rates	Durability	ASH guidelines, 2011	International Consensus, 2010
Prednisone 0.5-2 mg/kg/d for 4 wk	70-80%	10-30%	Recommended	Standard approach
Dex 40 mg/d on days 1-4 x 4 cycles	60-70%	50%	Feasible, longer courses are preferred	Standard approach
IVIg 0.8-1 g/kg/d for 1-2 d	80%	4 wk	-if steroids contraindicated - if rapid PLT response is required	-More rapid response -Higher toxicities
Dex + RTX	70-80%	58%	Investigational	Investigational

Neunert CE, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117(16): 4190-4207. Provan D et al, International Consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-186.

- **La piastrinopenia immune è “guaribile”?**
- **La terapia di seconda linea è in grado di “guarire” l’ITP?**

Trattamento di II linea: raccomandazioni internazionali

Intervention	Initial response rates	Durability	ASH guidelines	International Consensus
Splenectomy	80%	66%	Recommended *Laparoscopic, vaccinations*	Individual judgment (defer 6-12 mos)
Rituximab	50-60%	20-40%	Not recommended *May be considered for patients at risk of bleeding*	Individual judgment
TPO-R agonists	80%	50-60%	Not recommended *May be considered for patients at risk of bleeding*	Individual judgment (maintenance therapy)
Azathioprine, Cyclosporin A Cyclophosphamide Mycophenolate Other	20-80%	20-40%	Not recommended *May be considered*	Individual judgment (maintenance therapy)

Neunert CE, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117(16): 4190-4207. Provan D et al, International Consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-186.

Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications

Risposta estrapolata da casistiche comprendenti pazienti adulti, osservati per almeno 5 anni

- **Risposta completa 456/707 (64%) pazienti**
- **Ricaduta 15% (alcune casistiche comprendenti adulti+bambini; f-up mediano 33 mesi)**

Kojouri K et al, Blood 2004

Complicanze Post Splenectomia

	LAPAROTOMIA	LAPAROSCOPIA
MORTALITA'	1% (48/4955)	0.2% (3/1301)
CAUSE		
Emorragia	11	1
Cardiovascolare	10	1
Infezione	6	1
Tromboembolia	5	-
Altre	6	-
Sconosciuta	10	-
COMPLICANZE %	12.9 (318/2465)	9.6 (88/921)

Kojouri K et al, Blood 2004

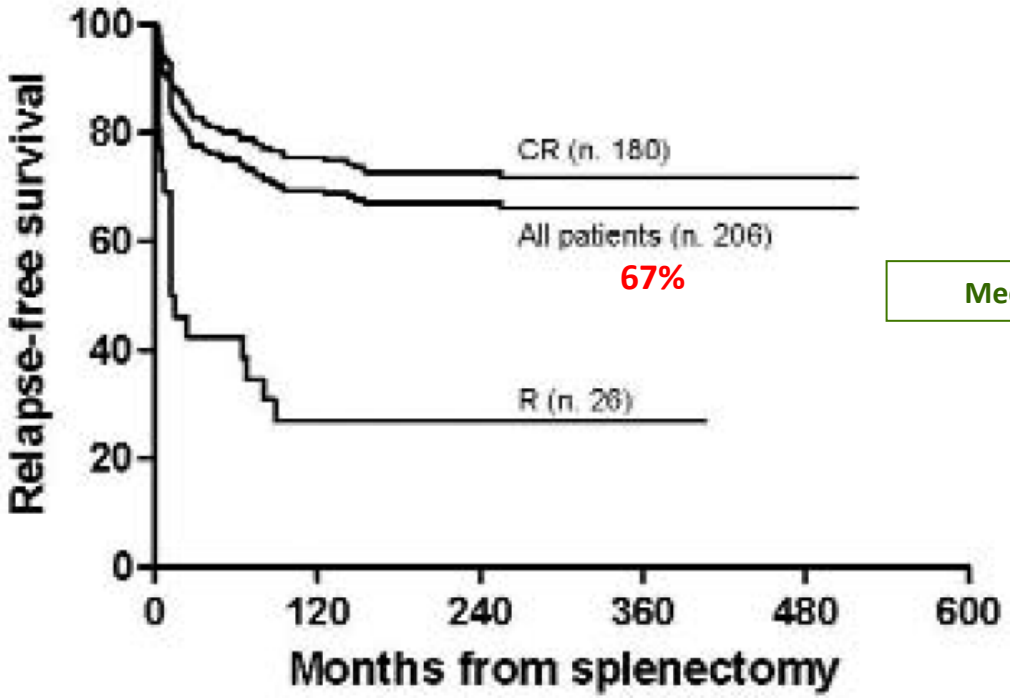
Table 3. Prediction of response to splenectomy

Variable	Predictive no. of articles (no. of patients)	Not predictive no. of articles (no. of patients)
Preoperative		
Age	14 (1185)	14 (913)
Sex	1 (26)	22 (1830)
PTI duration	2 (86)	27 (2346)
Response to steroids	11 (923)	19 (1424)
Response to IVIg	3 (154)	7 (333)
PLT count	4 (264)	9 (750)
Site of PLT sequestration	6 (566)	8 (480)
Postoperative		
PLT count	10 (868)	7 (357)

Adapted from Kojouri et al, Blood 2004

Splenectomy as a curative treatment for immune thrombocytopenia: a retrospective analysis of 233 patients with a minimum follow-up of 10 years

Nicola Vianelli,[1]* Francesca Palandri,[1]* Nicola Polverelli,[1] Roberto Stasi,[2] Joel Joelsson,[3] Eva Johansson,[3] Marco Ruggeri,[4] Francesco Zaja,[5] Silvia Cantoni,[6] Angelo Emanuele Catucci,[2] Anna Candoni,[5] Enrica Morra,[6] Magnus Björkholm,[3] Michele Baccarani,[1] and Francesco Rodeghiero[4]



Median f-up from splenectomy 20 yrs (10-43)

Figure 1. Relapse-free survival (RFS). RFS was 67% (95% CI: 61.3%-74.1%) for all responding patients, 73% (95% CI: 66.2%-79.5%) for CR patients and 27% (95% CI: 10%-43%) for R patients (P<0.001). CR: complete response (PLT>100x10^9/L). R: Response (PLT 30-100x10^9/L).

haematologica | 2013; 98(3)

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Outcome of refractory patients	*Overall*	Non-responding	Relapsing
No. of patients (%)	*95/233 (41%)*	27/233 (11.5%)	68/206 (33%)
Spontaneous response, no (%)	*3 (3%)*	0	3
Further medical therapy, no. (%)	*92/95 (97%)*	27/27 (100%)	65/68 (95%)
Median no. of therapies, (range)	*2 (1-12)*	2 (1-12)	2 (1-11)
Response to post-splenectomy treatments, no. of patients (%)			
CR (PLT>100x10^9/L)	*53/92 (58%)*	16/27 (59%)	37/65 (57%)
R (30-100x10^9/L)	*23/92 (25%)*	8/27 (30%)	15/65 (23%)
NR (<30x10^9/L)	*16/92 (17%)*	3/27 (11%)	13/65 (20%)
No of patients needing a continuative treatment to maintain a response (R or CR) (%)	*25/92 (27%)*	9/27 (33%)	16/65 (25%)

Splenectomy as a curative treatment for immune thrombocytopenia: a retrospective analysis of 233 patients with a minimum follow-up of 10 years

Table 4. Long-term complications.

	N. of events (%)	All patients (233)	Refractory patients (95)	Stable responders (138)	P
Infections					
Lung	63 (40%)	41 (18%)	23 (24%)	18 (13%)	0.03
Gastrointestinal/ urogenital/skin	41 (26%)	21 (9%)	13 (14%)	8 (6%)	0.06
Other (minor recurrent infections)	53 (33%)	28 (12%)	14 (14.5%)	14 (10%)	0.31
Fatal (sepsis)	2 (1%)	2 (1%)	1 (1%)	1 (0.7%)	1.00
Overall	159 (100%)	73 (31%)	40 (42%)	33 (24%)	0.004
Thrombosis					
Stroke/TIA	4 (15.5%)	4 (2%)	2 (2%)	2 (1.4%)	1.00
DVT/PE	12 (46%)	8 (3.5%)	4 (4%)	4 (2.8%)	0.71
AMI	6 (23%)	6 (2.5%)	4 (4%)	2 (1.4%)	0.22
Fatal (2 strokes + 2 AMI)	4 (15.5%)	4 (2%)	3 (3%)	1 (0.7%)	0.30
Overall	26 (100%)	18 (8%)	10 (10.5%)	8 (6%)	0.21
Hemorrhage					
Grade 1-2	221 (92%)	47 (20%)	41 (43%)	6 (4%)	<0.0001
Grade 3-4	17 (7%)	16 (7%)	13 (14%)	3 (2%)	<0.0001
Fatal (intracranial)	3 (1%)	3 (1.2%)	3 (3%)	0 (0%)	<0.0001
Overall	241(100%)	58 (25%)	49 (51.5%)	9 (6.5%)	<0.0001

TIA: transient ischemic attack. DVT: Deep vein thrombosis; PE: Pulmonary embolism; AMI: acute myocardial infarction.

Vianelli et al.

haematologica | 2013; 98(3)

Safety and efficacy of splenectomy in over 65-yrs-old patients with immune thrombocytopenia

Gonzalez-Porras JR
Eur J Haematol 2013

- 161pz età <65aa; 57pz età ≥65aa
- Migliore % di CR (84 vs 72%) e minore % di ricaduta (29 vs 43%) nei pz con età <65aa vs ≥ 65aa
- 60% dei pazienti mantiene la risposta a distanza di 14 anni dall'intervento
- Un numero ≤ 2 di trattamenti pre spl e un picco della conta PLT ≥ $250x10^9$/L nei giorni successivi all'intervento, impatta positivamente sulla probabilità di risposta duratura
- L'età particolarmente avanzata influenza negativamente la probabilità di complicanza post splenectomia.
- La via laparoscopica è più sicura

- Osservazione mediana 85 e 62 mesi rispettivamente, per età ≤ 65 e >65 anni
- **Mortalità 1.6% nei pazienti più anziani**

Clinical Outcome and Predictive Factors in the Response to Splenectomy in Elderly Patients with Primary Immune Thrombocytopenia: A Multicenter Retrospective Study

Park YH et al. Acta Haematologica 2016

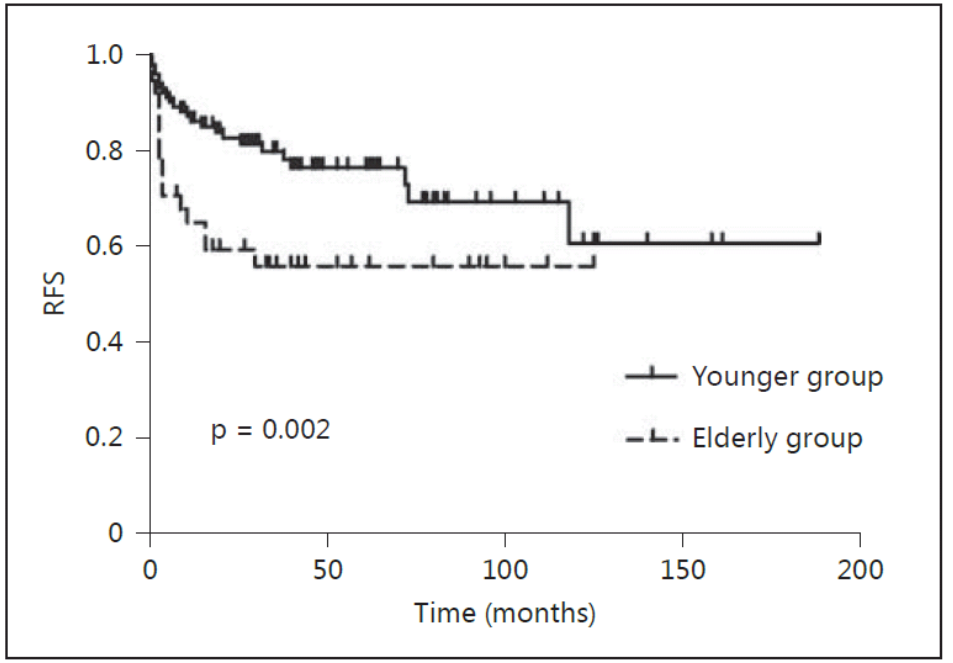


Fig. 3. Kaplan-Meier curve of RFS according to age group.

Table 3. Response after splenectomy

	Overall (n = 184)	Younger group (n = 132)	Elderly group (n = 52)	p
CR	124 (67.4)	92 (69.7)	32 (61.5)	0.288
R	24 (13.0)	14 (10.6)	10 (19.2)	
NR	33 (17.9)	24 (18.2)	9 (17.3)	
Not available	3 (1.6)	2 (1.5)	1 (1.9)	
Overall response (CR+R)	144 (80.4)	106 (80.3)	42 (80.7)	0.466
Relapse	43 (29.1)	24 (22.6)	19 (45.2)	0.006

Values are n (%).

Clinical Outcome and Predictive Factors in the Response to Splenectomy in Elderly Patients with Primary Immune Thrombocytopenia: A Multicenter Retrospective Study

Park YH et al. Acta Haematologica 2016

Table 4. Postoperative complications according to age group

	Overall (n = 184)	Younger group (n = 132)	Elderly group (n = 52)	p
Early complications (within POD 30)	19 (10.3)	9 (6.9)	10 (19.2)	0.013
Bleeding	14 (7.6)	7 (5.3)	7 (13.5)	0.060
Infection	3 (1.6)	1 (0.8)	2 (3.8)	0.036
Cardiovascular event	2 (1.1)	1 (0.8)	1 (1.9)	0.492
Mortality within POD 30	1 (0.5)	0 (0.0)	1 (1.9)	0.110
Late complications (POD 31–100)	16 (8.7)	6 (4.5)	10 (19.2)	0.001
Thrombosis	8 (4.3)	2 (1.5)	6 (11.5)	0.001
Infection	6 (3.3)	4 (3.0)	2 (3.8)	0.382
Bleeding	2 (1.1)	0 (0.0)	2 (3.8)	0.005
RBC transfusions	0 (0–15)	0 (0–15)	0 (0–10)	0.160
Postoperative stay, days	8 (4–60)	7 (4–60)	9.5 (4–52)	0.019

Values are medians (range) or n (%). RBC = Red blood cell.

Table 5. Multivariate analysis of the elderly patients related to response to splenectomy

Variable	HR	95% CI	p
A responder to any therapies prior to splenectomy	2.902	1.238–6.803	0.014
Postoperative platelet count >200 × 10^9/l	31.429	4.146–238.275	0.001

blood

2013 121: 4782-4790
Prepublished online May 1, 2013;
doi:10.1182/blood-2012-12-467068

Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia

Soames Boyle, Richard H. White, Ann Brunson and Ted Wun

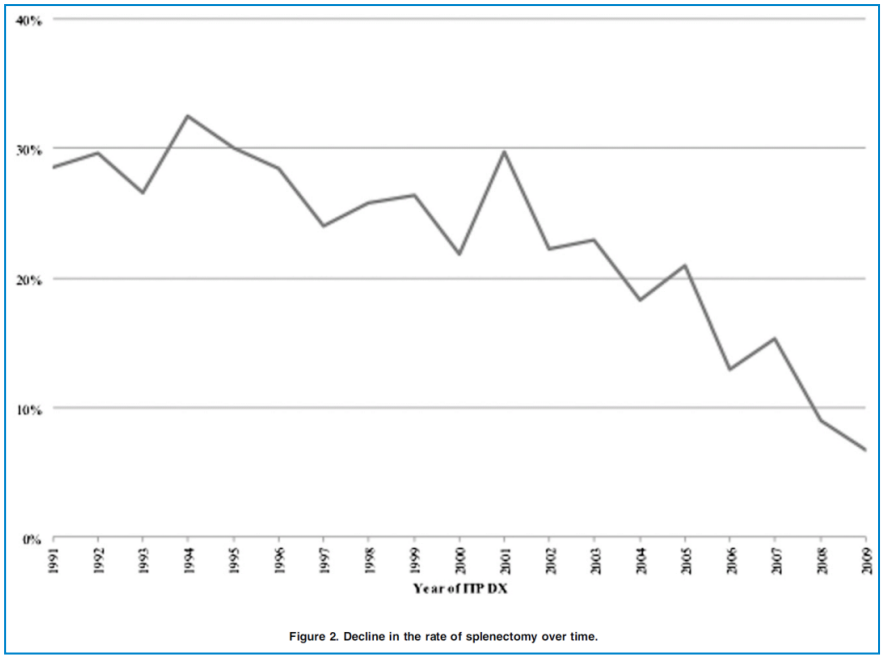


Figure 2. Decline in the rate of splenectomy over time.

La splenectomia garantisce la maggiore probabilità di risposta duratura (guarigione?), tuttavia:

- **Impredittività della risposta**
- **Riluttanza ad eseguire un intervento chirurgico maggiore, in un paziente spesso con marcata piastrinopenia**
- **Riluttanza da parte del paziente a sottoporsi a procedura invasiva, per togliere organo che ha una sua funzione**
- **Rischio di complicanza infettiva o trombotica, sebbene di entità relativamente bassa, ma non ancora ben definita**

La splenectomia

Pro

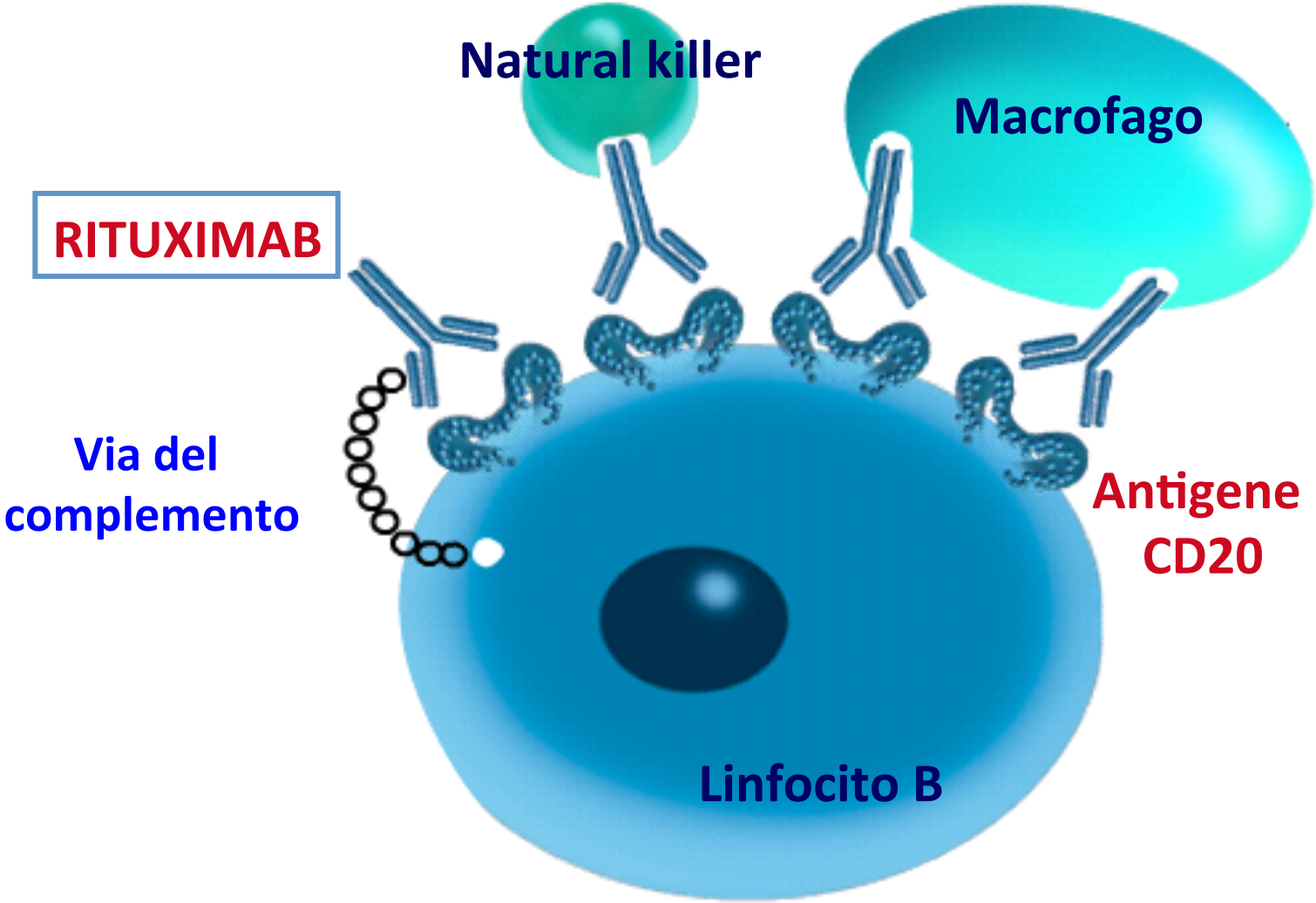
1. E' a tutt'oggi la terapia che garantisce il miglior risultato nel lungo termine
2. I rischi chirurgici (già bassi), possono essere ulteriormente ridotti in modo significativo, dall'utilizzo della via laparoscopica vs laparotomica
3. Fattibilità anche nell'anziano
4. L'incidenza di complicanze infettive post splenectomia può essere ridotta da:
   - Vaccinazione
   - Profilassi antibiotica

Contro

1. Riluttanza a rimuovere un organo "sano"
2. Timore delle complicanze chirurgiche e non
3. Mancanza di fattori prognostici affidabili, in grado di distinguere i pazienti potenzialmente guaribili
4. Disponibilità di nuovi presidi terapeutici:
   - Anticorpi monoclonali anti CD20
   - TPOm di seconda generazione

MECCANISMO D'AZIONE

Attività citotossica complemento e cellulo - mediata



Patel VL et al. Blood 2012

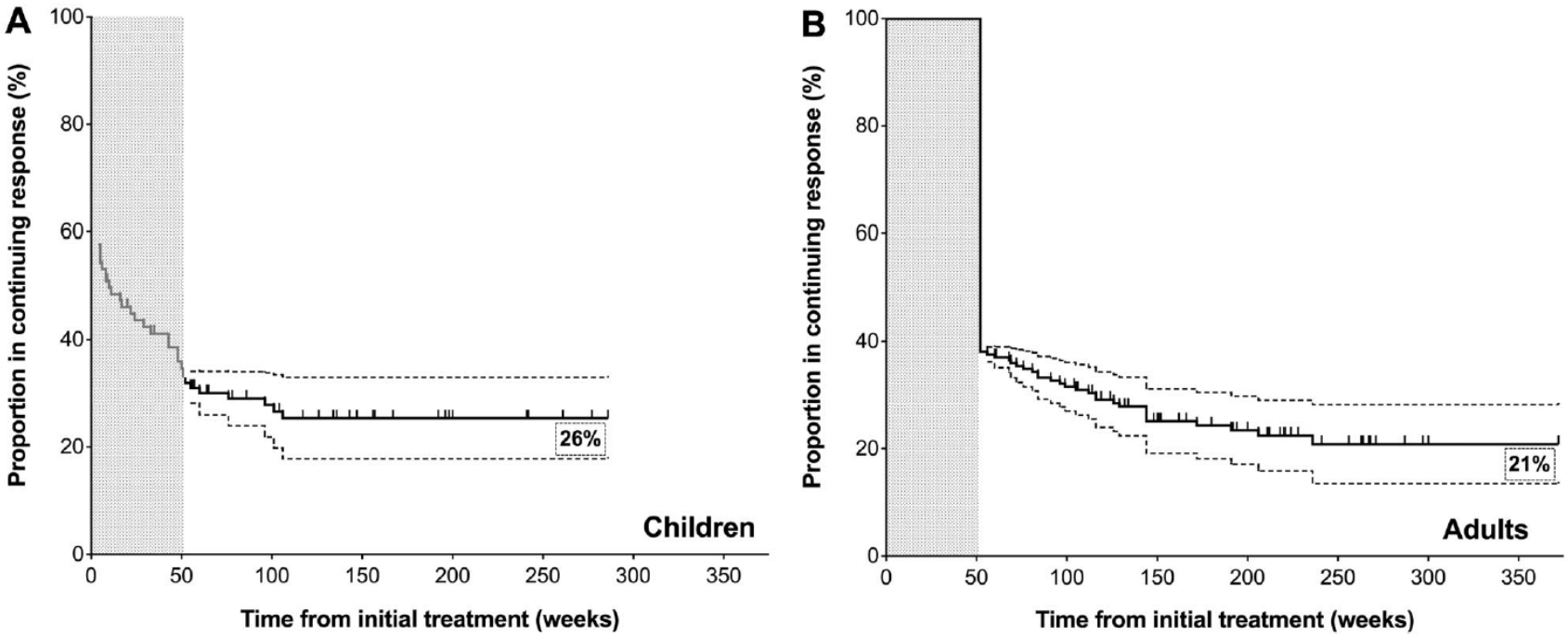


Figure 2. Response duration in all children who responded to rituximab (however transiently) and adults whose response lasted at least 1 year since treatment. Kaplan-Meier estimates of response to rituximab past 1 year in (A) children (n = 38) and (B) adults (n = 72). Vertical lines along the Kaplan-Meier curve indicate the last follow-up of an ongoing response. Adult long-term response rate projection originated at 1 year, 38%, based on published reports (Figure 1). Children's long-term response rate projection originated at 1 year, 33%, based on published reports and data presented in this study (gray line; Figure 1). Error bars (dotted lines) represent the 95% confidence intervals of response projections.

• Considerati 17 studi pubblicati/486pz (376 adulti, 110 bambini), per definire l'entità della **risposta iniziale** al Rituximab:
57% negli adulti e 56% nei bambini

• Considerati i "responders" iniziali e utilizzando poi i dati di Godeau per gli adulti e l'analisi di Kaplan-Meier per i 66 bambini, ne deriva che a 1 anno il 38% e a 2 anni il 30% sia degli adulti che dei bambini mantiene la risposta, mentre
a 5 anni il 21% degli adulti e il 26% dei bambini mantiene la risposta.

Long-term follow-up analysis after rituximab salvage therapy in adult patients with immune thrombocytopenia

Francesco Zaja,[1]* Stefano Volpetti,[1] Marianna Chiozzotto,[1] Simona Puglisi,[1] Miriam Isola,[2] Silvia Buttignol,[1] and Renato Fanin[1]

Zaja F et al. Am J Hematol, 2012

TABLE 2. Response Rate and Outcome after Rituximab Therapy

	All patients	Standard dose rituximab	Low dose rituximab
Patients	57	32	25
OR (%)	34 (60)	21 (66)	13 (52)
CR (%)	23 (40)	16 (50)	7 (28)
NR (%)	23 (40)	11 (34)	12 (48)
Median time to response, days (range)	14 (7–120)	10.5 (7–120)	30 (7–100)
Median time to CR, days (range)	45.5 (7–150)	40 (7–150)	30 (7–150)
Relapse (%)	15 (44)	8 (38)	7 (54)
Relapse after CR (%)	7 (30)	6 (37.5)	1 (14)
Median RD, months (range)	24 (3–120)	26.5 (3–120)	22 (3–52)
Median follow-up, months (range)	52 (3–144)	82 (3–144)	44 (13–63)
Long-term response (%)	19 (33)	13 (41)	6 (24)

OR, overall response; CR, complete response; RD, response duration. OR includes CR + PR.

Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients

Khellaf M et al. Blood 2014

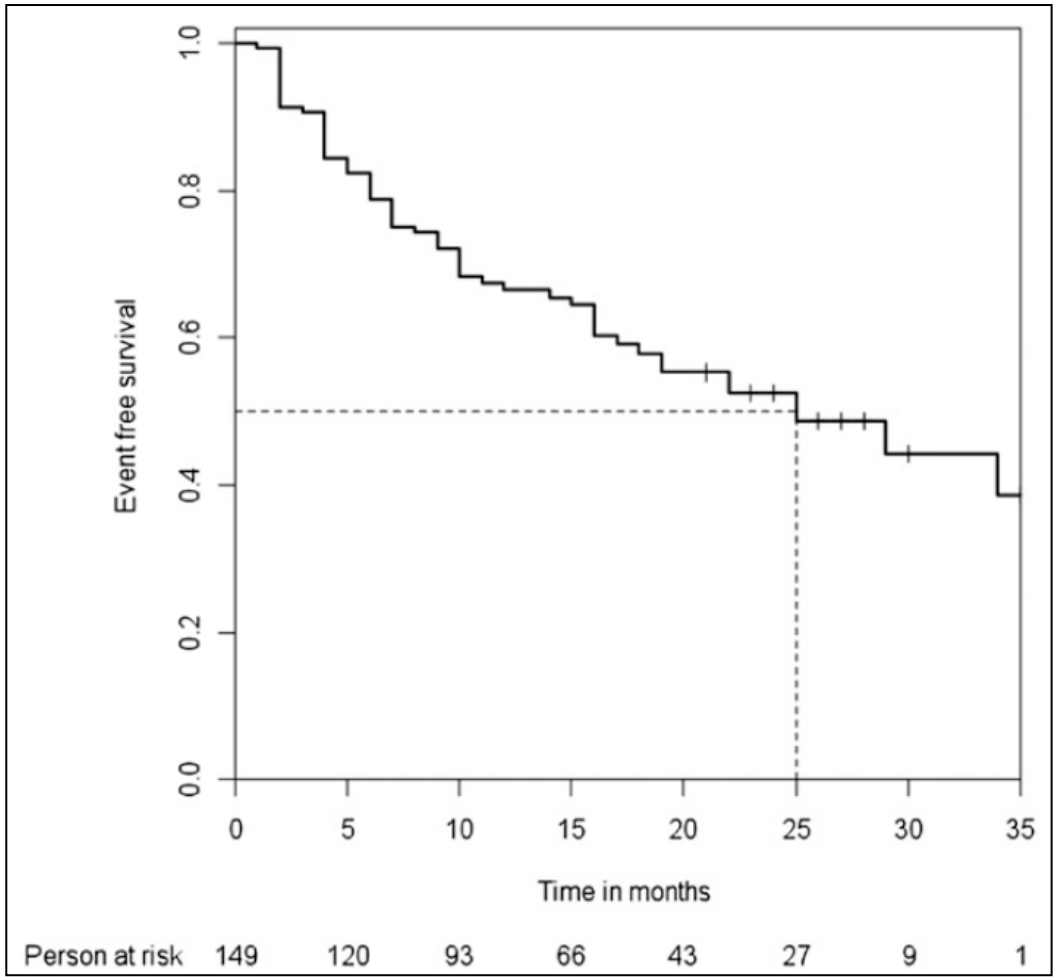
Table 1. Characteristics of adult patients with ITP treated with rituximab in the "ITP-ritux registry" in France

Patient characteristics	
Sex (F/M)	159/89 (F: 64%)
Age (y) at ITP diagnosis, mean ± SD	51 ± 20
Duration of ITP (months), median (Q1-3)	16 (5-72)
<1 y	102 (41%)
≥1 y	146 (59%)
Platelet count at ITP diagnosis ($\times 10^9$/L), median (Q1-3)	18 (6-41)
Lower platelet count in the month preceding first rituximab infusion ($\times 10^9$/L), median (Q1-3)	17 (7-25)
Bleeding signs on ITP diagnosis	
None	139 (56%)
Bleeding	109 (44%)
No. of previous treatments for ITP, median (Q1-3)	3 (2-4)
Previous treatment	
Steroids	240 (97%)
IVIG	175 (71%)
Splenectomy	25 (10%)
Rituximab regimens	
4 weekly infusions (4 × 375 mg/m^2)	173 (70%)
2 fixed 1-g infusions (2 wk apart)	72 (29%)
Other	3 (1%)
Premedication with methylprednisolone	233 (94%)
Dose of methylprednisolone (mg), median (Q1-3)	63 (40-100)
Follow-up duration (mo), median (Q1-3)	24 (12-30)
No. of patients with follow-up >12 mo	230 (93%)

F, female; IVIG, intravenous immunoglobulins; M, male.

Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients

Khellaf M et al. Blood 2014



- F-up mediano 24 mesi
- risposta iniziale 152/248 (61%) pz
- risposta duratura 96/248 (39%) pz
- 2.3 infezioni/100pz-anno
- Probabilità di risposta mantenuta a un anno, nei pz con breve storia di malattia e con risposta completa transitoria allo steroide

Figure 2. Median time to relapse. Median time to relapse among the 152 initial responders to rituximab therapy.

Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients

Khellaf M et al. Blood 2014

Table 2. Infectious complications after rituximab therapy for ITP

Sex, age (y)	Duration of ITP (mo)	Splenectomy before rituximab treatment	Site of infection	Infectious agents	Delay after first rituximab infusion, months	Admission to hospital/ parenteral antibiotics	Current treatment with steroids	Last gammaglobulin level (g/L)	Outcome
F, 38	16	No	Pulmonary	ND	2	−/+	No	NA	Recovery
M, 67	2	No	Cutaneous	ND	2	−/+	No	12.4	Recovery
F, 37	2	No	Pulmonary	*Streptococcus pneumoniae*	18	+/+	No	10.2	Recovery
M, 71	119	No	Flu-like syndrome	ND	4	−/−	No	NA	Recovery
M, 73	1	No	Bone, septic shock	*Aureus Staphylococcus*	13	+/+	Yes	NA	Death
M, 70	19	Yes	Pulmonary	*Enterococcus faecium*	12	+/+	Yes	5.4	Death
F, 74	2	No	Urinary tract	*Escherichia coli*	1	+/+	Yes	6.2	Recovery
			Sinus	*Aspergillus fumigatus*	2	−/+	Yes	6.2	Recovery
			Pulmonary	ND	2.5	−/+	Yes	6.4	Recovery
			Urinary tract	*Streptococcus*, group D	4	−/+	Yes	NA	Recovery
			Septic shock	*Enterobacter cloacae*	14	+/+	Yes	NA	Death

NA, not available; ND, not determined.

Rituximab and three dexamethasone cycles provide responses similar to splenectomy in women and those with immune thrombocytopenia of less than two years duration

Bussel JB et al.
Haematologica 2014

Table 1. Patients' demographics.

Age	Overall Median=21 years Range=1-64 years	Pediatric	Median=12 years Range=1-17 years	n=26 (39%)
		Adult	Median=36 years Range=18-64 years	n=41 (61%)
Gender	Overall Male=30 Female=37	Pediatric	Male Female	n=12 (46%) n=14 (53%)
		Adult	Male Female	n=19 (46%) n=22 (53%)
Duration of ITP	Overall Median=13 months Range=0-286 months	Pediatric	Median=10 months Range=1-159 months	
		Adult	Median=16 months Range=1- 286 months	
Prior therapies	Overall Median=2 therapies Range=0-7 therapies	Pediatric Median = 2 therapies	None Corticosteroids IVIG Anti-D TPO-RA	n=2 n=19 n=20 n=12
		Range = 0-4 therapies	Romiplostim Eltrombopag Cytotoxic agents Anti-proliferative agents Splenectomy	n=3 n=0 n=1 n=0 n=1
		Adult	None Corticosteroids	n=3 n=34
		Median = 2 therapies	IVIG Anti-D TPO-RA	n=21 n=9
		Range = 0-7 therapies	Romiplostim Eltrombopag Cytotoxic agents Anti-proliferative agents Splenectomy	n=1 n=4 n=4 n=4 n=3

Corticosteroids: prednisone, methylprednisolone, dexamethasone; IVIG: intravenous immunoglobulin; Anti-D: anti-Rh(D) immunoglobulin (Winrho); TPO-RA: thrombopoietin receptor agonist - romiplostim, eltrombopag; cytotoxic: cyclophosphamide, rituximab; anti-proliferative: azathioprine, vincristine.

- 67 pz; 41 adulti
- Solo 5 pazienti mai trattati in precedenza

Rituximab and three dexamethasone cycles provide responses similar to splenectomy in women and those with immune thrombocytopenia of less than two years duration

Bussel JB et al.
Haematologica 2014

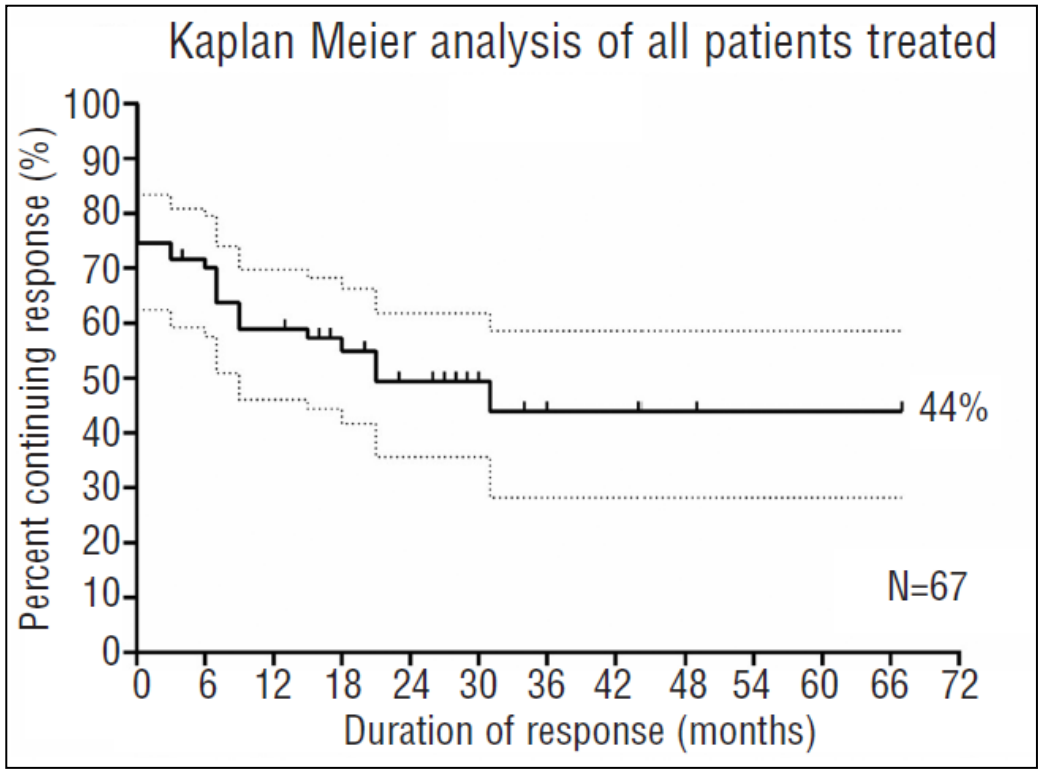


Figure 2. Long-term analysis of all patients treated with R+3Dex. Kaplan-Meier analysis estimates the long-term response to R+3Dex. Vertical marks indicate the last follow up of an ongoing response. 44% of the 67 patients treated were estimated to have a long-term response at more than five years from treatment. Eight responders maintain their treatment-free response a median of nine months past the last relapse.

- **Pz femmine con diagnosi <24mesi, hanno risposta duratura nel 60% dei casi**

Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial

Ghanima W et al. Lancet 2015

	Rituximab (n=55)	Placebo (n=54)
Median age, years	46 (27–61)	46 (28–60)
Female	40 (73%)	39 (72%)
Median platelet count, $\times 10^9$ cells/L	16 (6–27)	21 (9–29)
Median bleeding score*	2	4
Bleeding		
Petechiae	6 (11%)	7 (13%)
Mild blood loss	19 (35%)	23 (43%)
Gross blood loss	2 (4%)	2 (4%)
Treatment with corticosteroids	32 (58%)	24 (44)
Duration of ITP in weeks, median (IQR)	37 (8–288)	50 (14–211)
Newly diagnosed (0–3 months)	18 (33%)	12 (22%)
Persistent (3–12 months)	13 (24%)	16 (30%)
Chronic (>12 months)	24 (44%)	26 (48%)

Data are median (IQR) or n (%). ITP=immune thrombocytopenia. *Bleeding was also reported by a bleeding score.[16]

Table 1: **Baseline characteristics**

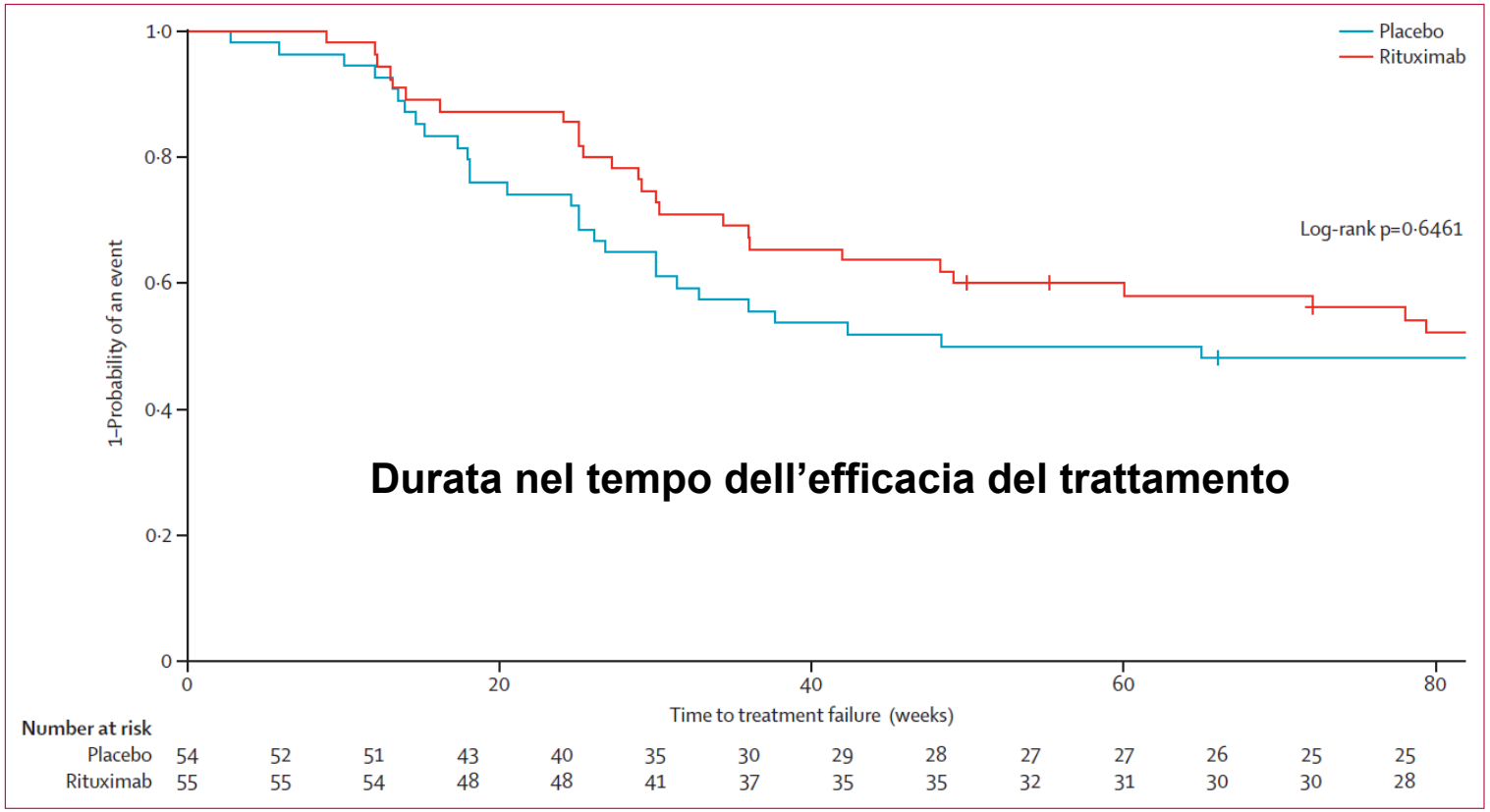
	Rituximab (n=55)	Placebo (n=54)	p value*
Efficacy outcomes			
Treatment failure within 78 wks	32 (58%)	37 (68%)	0·65
Splenectomy	8 (15%)	14 (26%)	0·12
Overall response	40 (73%)	36 (67%)	0·15
Loss of overall response	27 (68%)	28 (78%)	0·01
Median duration of overall response (weeks)	36 (13–not reached)	7 (5–69)	0·01
Complete response	28 (51%)	21 (39%)	0·12
Loss of complete response	14 (50%)	13 (62%)	0·19
Median duration of complete response (weeks)	76 (32–not reached)	49 (20–95)	0·19
Main safety outcomes			
Death	0	1 (2%)	NA
Bleeding	21 (38%)	27 (50%)	0·08
Infections	22 (40%)	13 (24%)	0·09
Venous thrombosis†	2 (4%)	0	NA

Data are n (%) or median (IQR). NP=testing was not done for difference in death and venous thrombosis because of the small number of events. *Log-rank p value estimated from survival analysis. †One pulmonary embolism and one deep venous thrombosis.

Table 2: **Number and simple rates of the efficacy and safety outcomes of the study**

Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial

Ghanima W et al. Lancet 2015



Durata nel tempo dell'efficacia del trattamento

Figure 3: **Time to treatment failure within 78 weeks**
The composite outcome of splenectomy or meeting criteria for splenectomy after week 12 if splenectomy was not done because of contraindications or patient's refusal.

- **Risposta duratura (>78 sett): - Rituximab 13/55 pz (24%)**
  - Placebo 8/54 pz (14%)
- **10 pz trattati, per ottenere una risposta duratura**

RITUXIMAB

PRO

- **Possibilità di risposta completa duratura sia nel paziente splenectomizzato che non splenectomizzato**
- **Possibilità di evitare/procrastinare la splenectomia**
- **profilo di tossicità più che accettabile**
- **Possibilità di utilizzo ripetuto, in caso di ricaduta a distanza di tempo**
- **Rischio/beneficio sostanzialmente favorevole, con risposta iniziale nel 50-60% dei casi**

CONTRO

- **Rischio riacutizzazione HCV/HBV**
- **Rischio infezioni non trascurabile, fino a 6-9 mesi dopo la somministrazione**
- **Leucoencefalopatia multifocale progressiva**
- **Scarsa "tenuta" della risposta nel tempo (mantenuta a 5aa nel 20-40% dei casi)**

Trattamento di III linea : raccomandazioni internazionali

Intervention	Initial response rates	Durability	ASH guidelines 2011	International Consensus 2010
TPO-R agonists	80%	50%	**Recommended, if splenectomy contraindicated or failed**	**Recommended**
Rituximab	50-60%	20-30%	Individual Judgment	Individual judgment
Azathioprine, Cyclosporin A Cyclophosphamide Mycophenolate Other	20-80%	20-40%	Individual judgment (maintenance therapy)	Individual judgment (maintenance therapy)

Neunert CE, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117(16): 4190-4207. Provan D et al, International Consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-186.

- **18/12/2009 Gazzetta Ufficiale: Nplate erogabile in fascia H, nei pz. Con ITP splenectomizzati refrattari ad altri trattamenti o in II linea quando splenectomia controindicata**

• **Romiplostim (Nplate) ed Eltrombopag (Revolade)** garantiscono una risposta iniziale nel **70-80%** dei casi, indipendentemente (?? Romiplostim??) dalla presenza o meno della milza e dai valori basali delle piastrine ♠

• La risposta si mantiene nel lungo termine in circa il **50-60%** dei casi

• La risposta si perde nel giro di 1-2 settimane alla sospensione del trattamento

• Esistono casi nei quali la risposta si mantiene anche dopo la sospensione del trattamento

• Eventi avversi in gran parte contenuti (tossicità epatica, aumento trama reticolinica midollare ossea) e reversibili con la sospensione del trattamento

♠ **Romiplostim:** risposta iniziale 79 spl vs 88% non spl; duratura 38 spl vs 61% non spl

TPO mimetici: domande per il futuro

- **Quali altre modalità d'impiego possibili, oltre a quelle per le quali i TPOm sono registrati?**

- **Risposta mantenuta anche dopo la sospensione del trattamento: come, quando, perché…..**

- **Ulteriori informazioni su efficacia del cross-over, nei pazienti refrattari o che hanno un difficile controllo della conta piastrinica con un TPOm**

- **Ulteriori dati su efficacia e tossicità nel lungo termine**

- **Maggiori informazioni su possibile associazione con farmaci immunosoppressori**

- **……..**

Patients' characteristics

	overall	years of diagnosis 1980-89	years of diagnosis 1990-99	years of diagnosis 2000-09	years of diagnosis 2010-15
No. of patients	***557***	106	133	223	95
Male/female (% male)	***208/349 (37%)***	37/69 (35%)	49/84 (37%)	88/135 (39%)	34/61 (36%)
Median age (range)	***51 (1-95)***	59 (16-78)	51 (2-80)	49 (1-76)	53 (19-95)
Median PLT , x10^9/l (range)	***15 (1-98)***	12 (2-43)	16 (1-86)	14 (1-65)	12 (1-98)
No. of treated patients (%)	***397 (71%)***	86 (81%)	92 (69%)	145 (65%)	74 (78%)
No of pts who started therapy ≥6 mos from dx (%)	***40 (10%)***	8 (9%)	12 (13%)	15 (10%)	5 (7%)
No. of patients treated with ≥4 lines (%)	***22 (5.5%)***	9 (10.4%)	4 (4.3%)	6 (4.1%)	3 (4%)
Median follow-up of living patients, years (range)	***6.9 (0.3-30)***	15.3 (0.3-30)	11.1 (0.3-25)	6.8 (0.3-14.8)	2.4 (0.3-5.2)

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Front-line treatment: predisone vs dexamethasone

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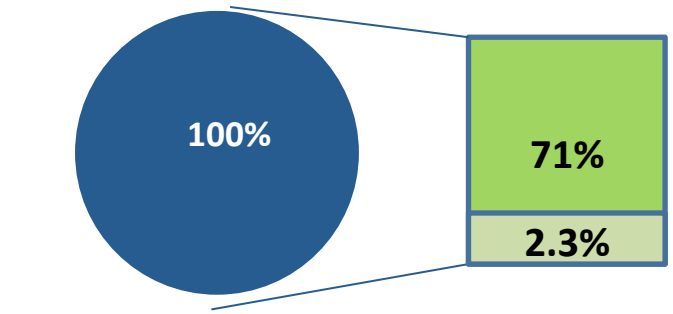
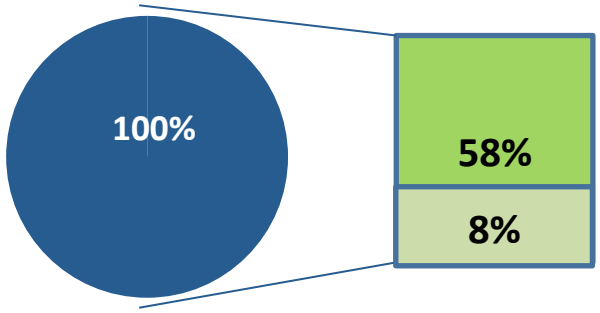
1980-89 (n.106)



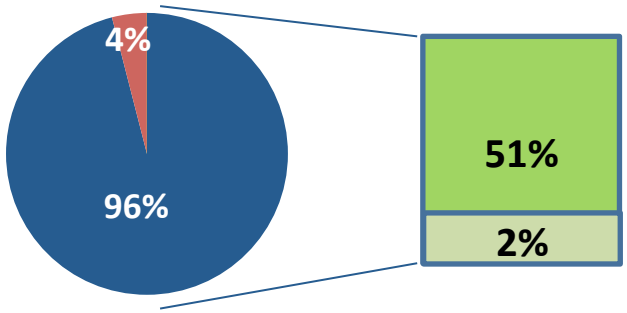
PDN DEX % relapse*

1990-99 (n.133)



PDN DEX % relapse

2000-09 (n.223)

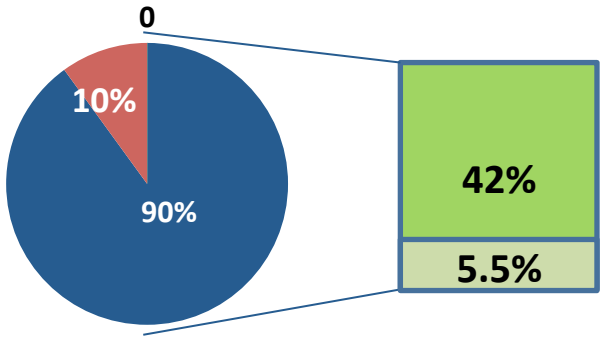


4 patients were treated with RTX + DEX front-line

PDN DEX % relapse

p = n.s.

2010-15 (n.95)



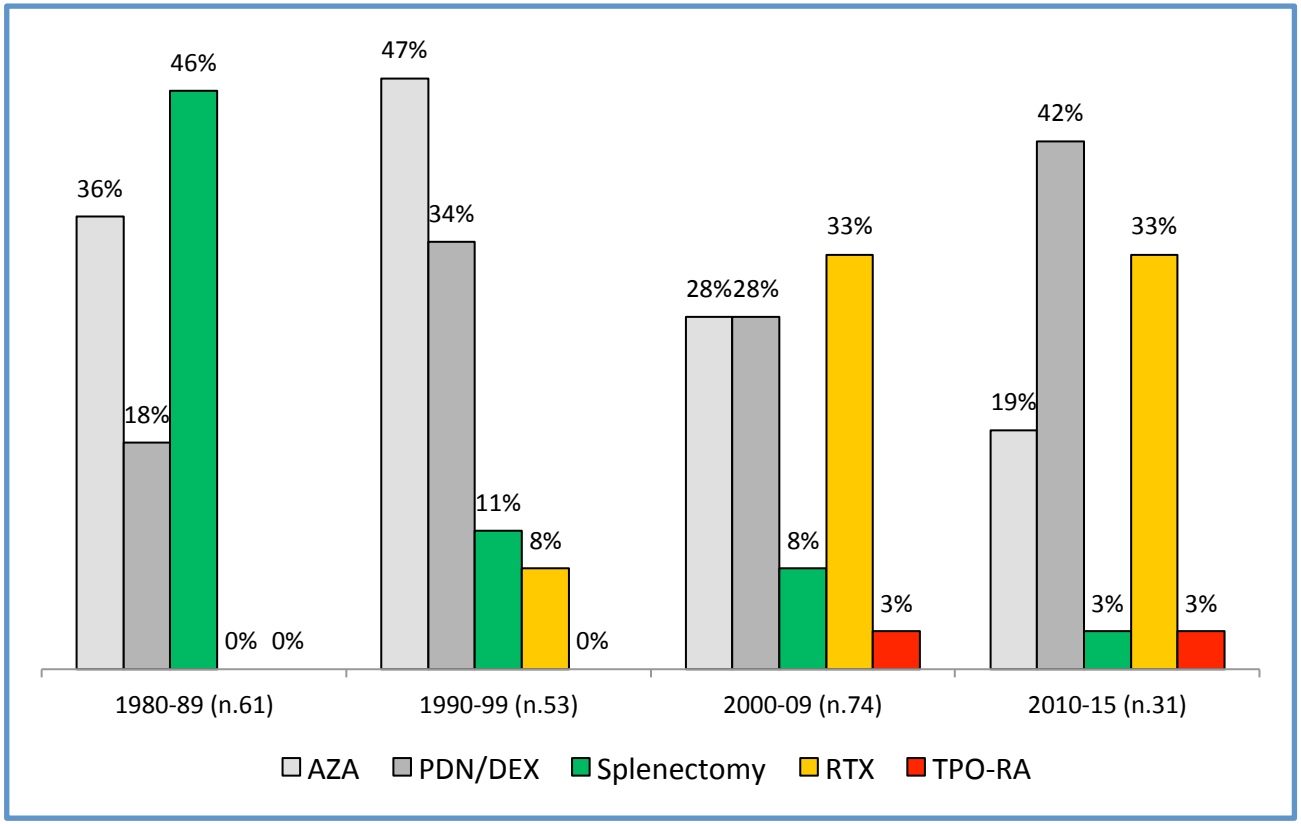
PDN DEX % relapse

** Includes patients who required a 2°-line therapy or continuous steroids administration*

Second-line treatments: changes over time

Overall, 219 out of 397 (55.2%) treated patients received a second line of therapy:

33.8%	*azathioprine (CSA, EDX, MMF)*	*(n.74)*
28.8%	*prednisone/dexamethazone*	*(n.63)*
18.7%	*splenectomy*	*(n.41)*
17.4%	*rituximab*	*(n.38)*
1.3%	*TPO-R agonists*	*(n. 3)*



Over the decades:

- AZA decreased (36% → 19%)
- STEROIDS increased (18% → 42%)
- **SPLENECTOMY** decreased (46% → 3%)
- **RTX increased** (0 → 33%)
- **TPO-RA** were used in selected cases

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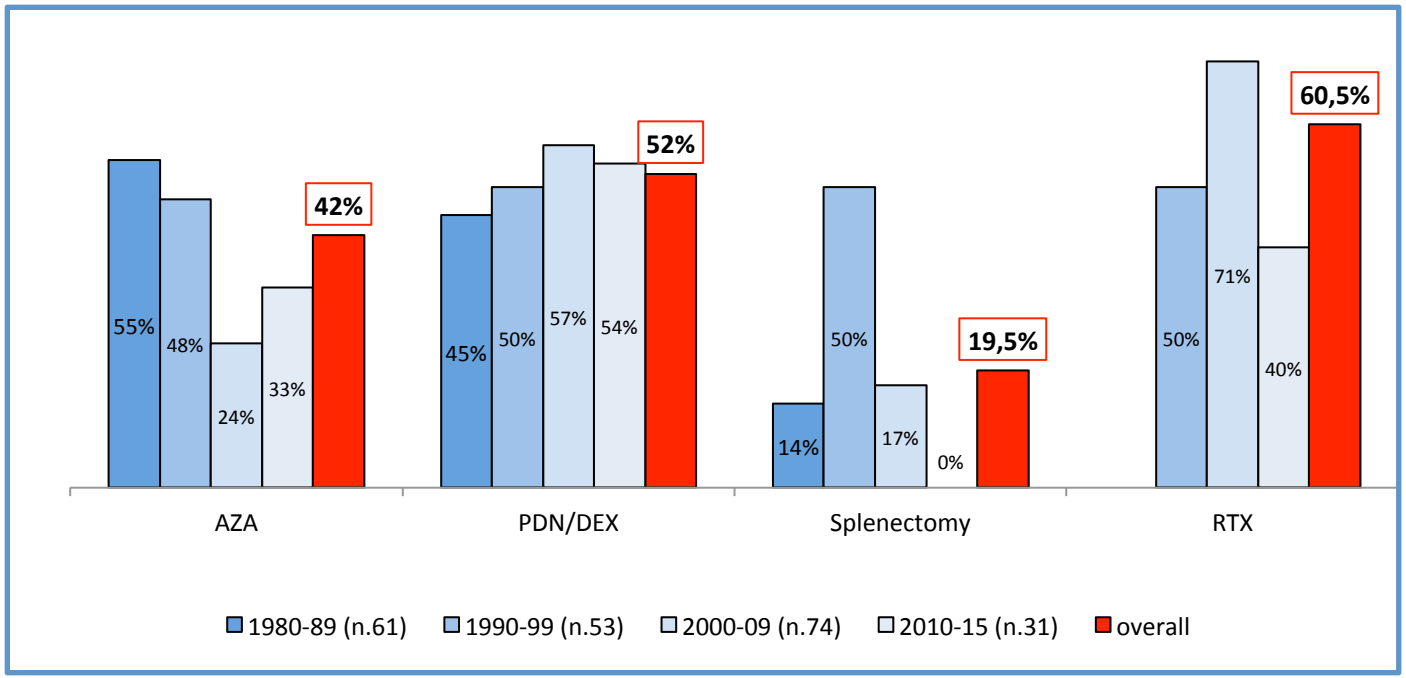
Second-line treatments: relapse rates over time



Relapse rate of splenectomy is significantly lower than all other therapies ($p<0.01$)

The relapse rate of RTX seems comparable to AZA and steroids

Overall, 96 out of 219 (43.8%) patients did not respond or relapsed after 2nd line therapy:

- *60.5%* *rituximab*
- *52.3%* *prednisone/dexamethazone*
- *42.1%* *azathioprine (CSA, EDX, MMF)*
- *19.5%* *splenectomy*

The 3 patients treated 2nd line with TPO-RA maintain a stable response on continuous therapy after 9, 12 and 36 months

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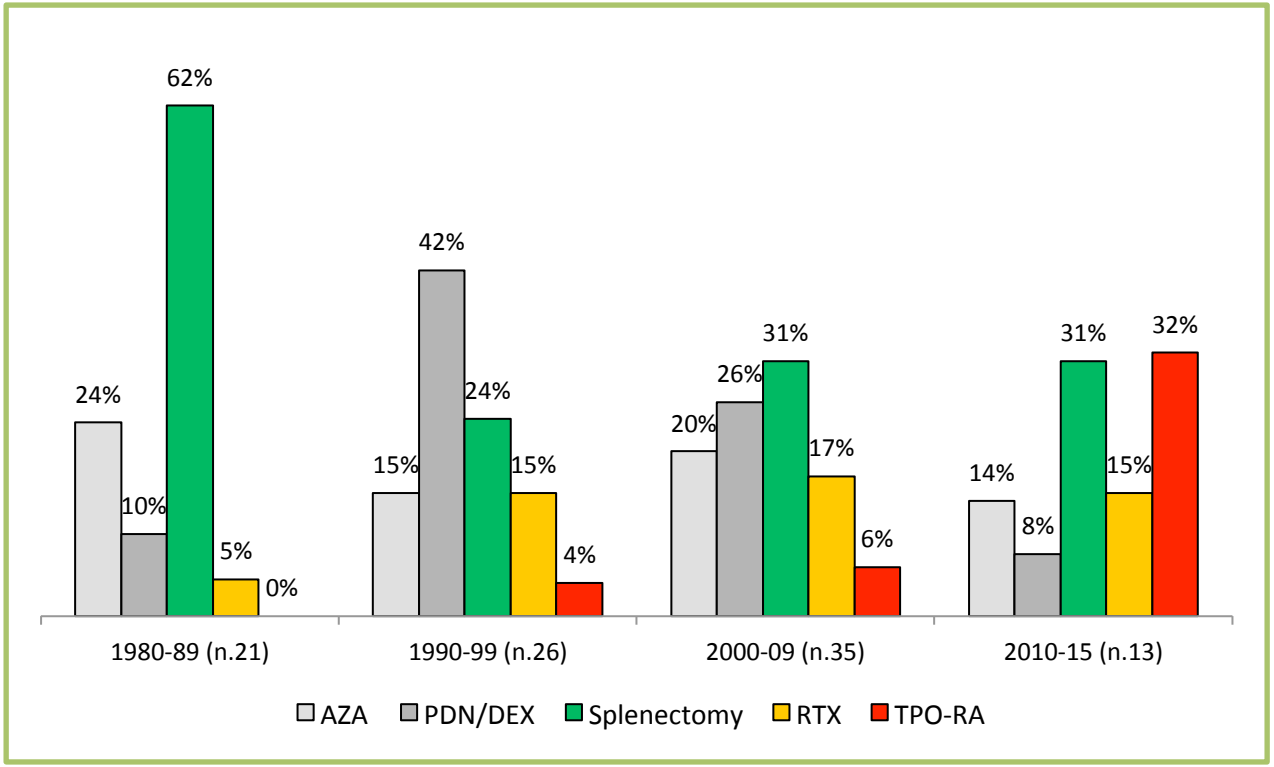
Third-line treatments: changes over time

Overall, 96 out of 219 (43.8%) pts treated 2nd line (24% of all treated pts) received a 3rd line therapy:

18.9%	azathioprine (CSA, EDX, MMF)	(n.18)
24.2%	prednisone/dexamethazone	(n.23)
35.8%	splenectomy	(n.34)
13.7%	rituximab	(n.13)
7.4%	TPO-RA	(n. 7)

22 pts (23%) required ≥4 therapies:

36% TPO-RA
27% azathioprine
23% prednisone
9% RTX
5% splenectomy



Over the decades:

- AZA remained stable, with mild decrease
- STEROIDS stable
- SPLENECTOMY decreased but still used in over 25%
- RTX stable (15-20%)
- TPO-RA were the most used in the last decades (small cohort)

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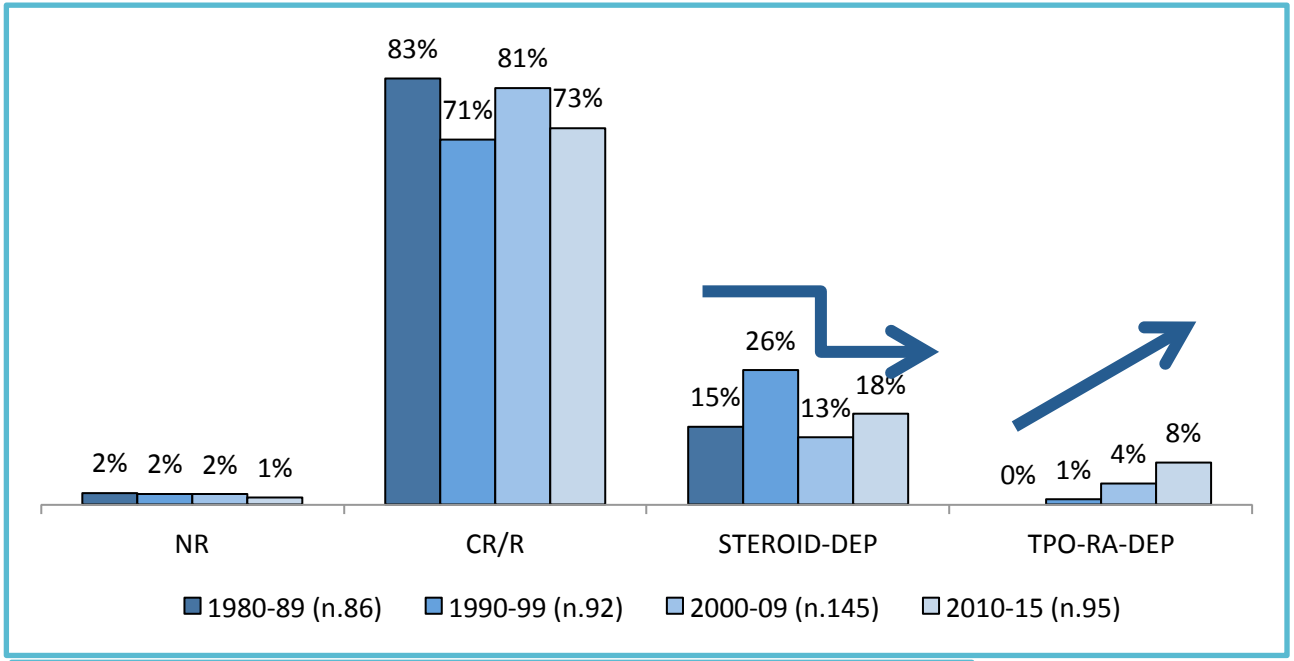
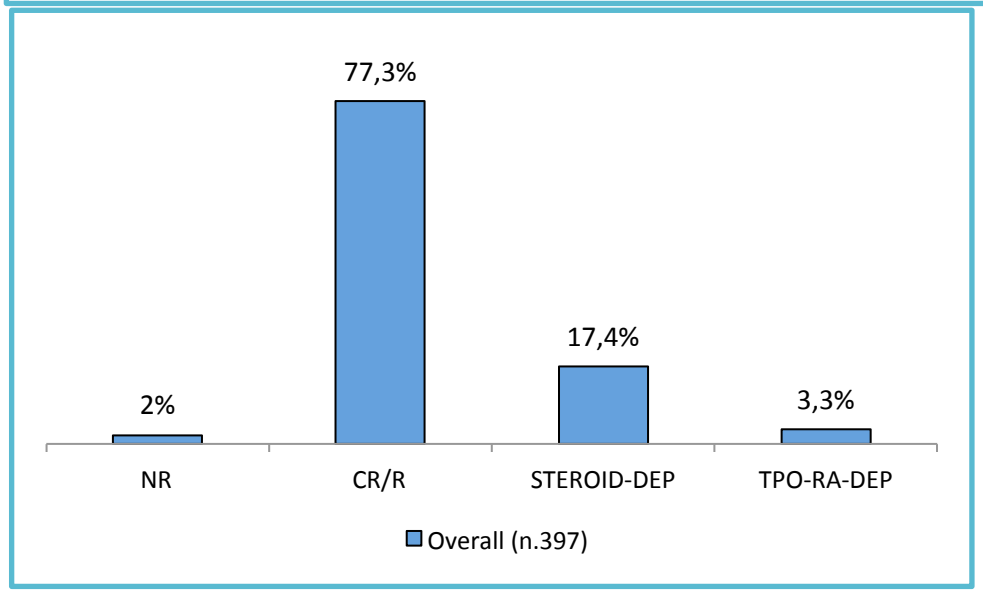
Overall responses over time: last evaluation



- The proportion of patients in response was stable over time
- A slight decrease in steroid-dependent responses was observed
- The proportion of patients with TPO-RA dependent responses is increasing over time



- At last follow-up, >95% of patients were in response
- However, in over 20% of the cases, the response was dependent to a chronic drug administration

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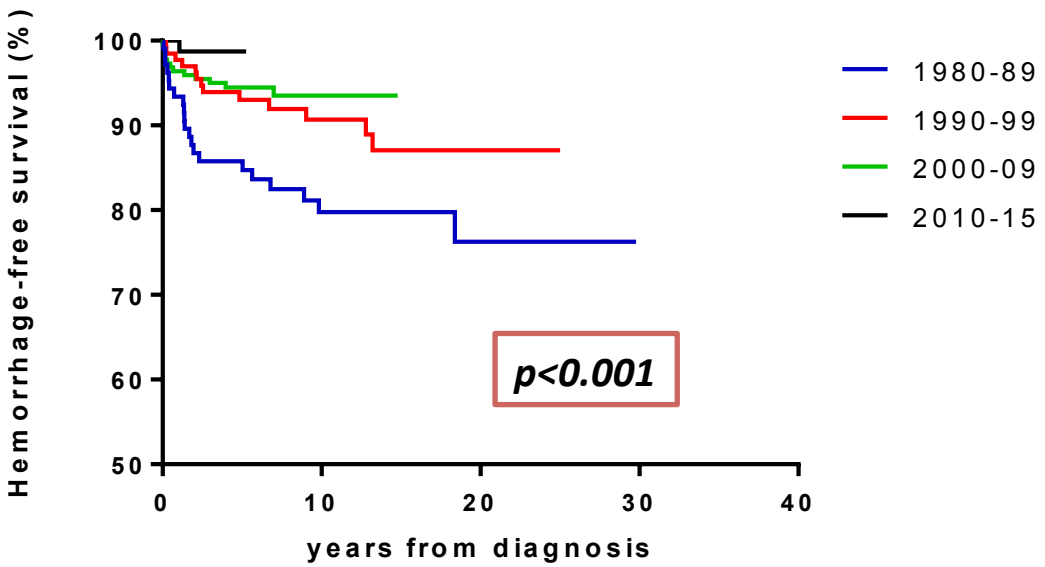
The issue of hemorrhages ≥Grade2 over time



The probability of hemorrhage decreased over time, mainly due to a lower rate of hemorrhages during the first 3 years from diagnosis.
Possible explanations:

- ***Better 1st line management?*** *(optimization of steroids administration)*
- ***Better 2nd line management?*** *(availability of RTX and TPO-RA)*
- ***Better management of chronic ITP?*** *(reduction of thrombocytopenia duration?)*

Sixty-three hemorrhages ≥Grade2 were recorded in 47 (8.4%) patients, for an incidence rate of 1.06%patient/year.
At 5 years, the cumulative risk of bleeding was 14.3% (1980-89), 7% (1990-99), 5.6% (2000-09) and 1.2% (2010-15) (p<0.001)

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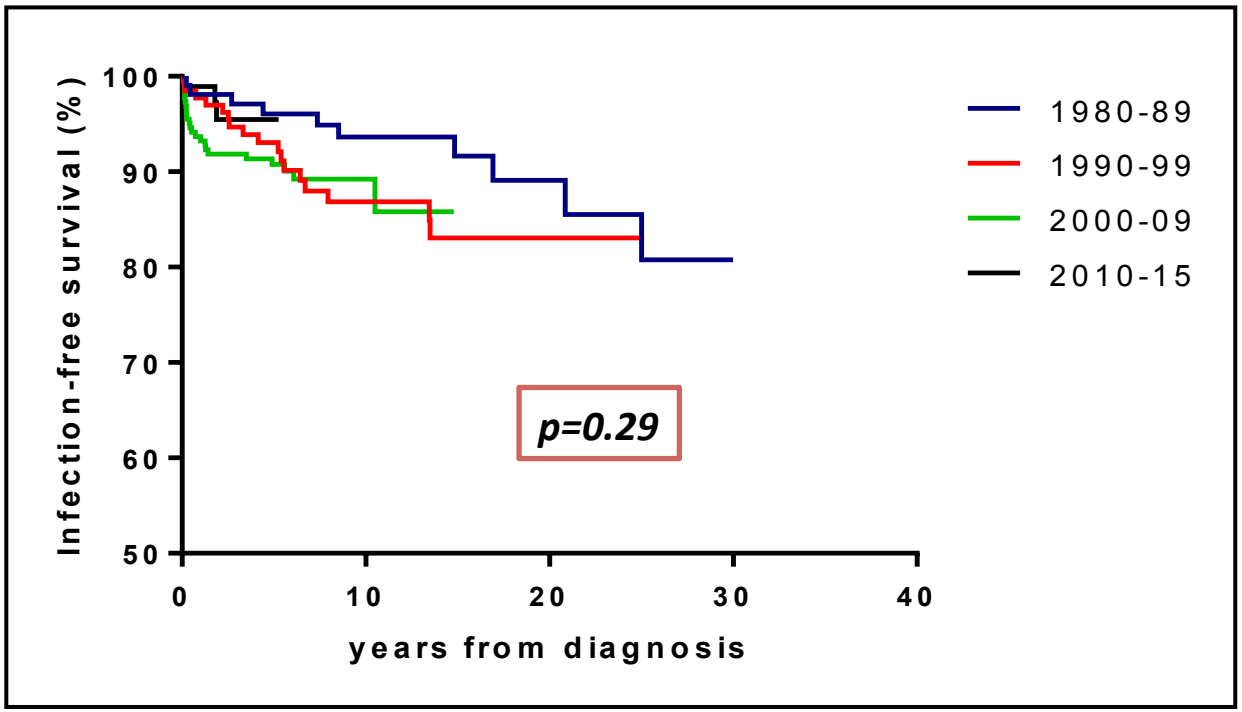
The issue of infections over time



The probability of infections did not increase over time, despite the different observation time, probably due to a higher vaccination rate

- Infections occurred in 53 patients (9.5%), for an incidence rate of 1.16% patient/year.
- At 5 years, the cumulative risk of infections was 4% (1980-89), 7% (1990-99), 9.3% (2000-09), 4.6% (2010-15) (p=0.29)

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Conclusioni

1. Nei decenni la splenectomia è passata dalla II alla III linea
   - *Rimane tuttavia utilizzata nel 10-15% dei pazienti*
   - *Garantisce la più alta % di successo sia in II che III linea*

2. Dagli anni 2000 il Rituximab è emerso come trattamento di scelta nella II e III linea
   - *Tuttavia, la % di ricaduta risulta significativamente alta*
   - *L'incidenza di complicanze infettive di grado ≥ 2 non è aumentata, nonostante l'aumento di utilizzo del farmaco; oltre l'80% dei pazienti trattati con RTX sono stati vaccinati*

3. Negli ultimi 5 anni i TPO-ra hanno superato il Rituximab, come prima scelta nella III linea di trattamento
   - *Rappresentano circa il 3% delle risposte farmaco dipendenti*

4. La % delle risposte globali e farmaco dipendenti, non è aumentata nelle decadi
   - *Tuttavia, l'incidenza di emorragie ≥ grado 2 è progressivamente calata, probabilmente grazie ad una migliore pratica clinica*

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