Integrazione dei nuovi farmaci nel programma trapiantologico : un caso clinico

Nuovi Farmaci e Trapianto, Udine 21-22 gennaio 2016

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Anamnesi

- Paziente di 58 anni , sesso f.
- In anamnesi :
  - Ulcere trofiche AAII dall'eta di 19 anni
  - Safenectomia bilaterale
  - Tiroidectomia subtotale
  - Trombofilia genetica : doppia eterozigosi G169A e H1299 fattore V e doppia eterozigosi C677T e A1298C MTHFR

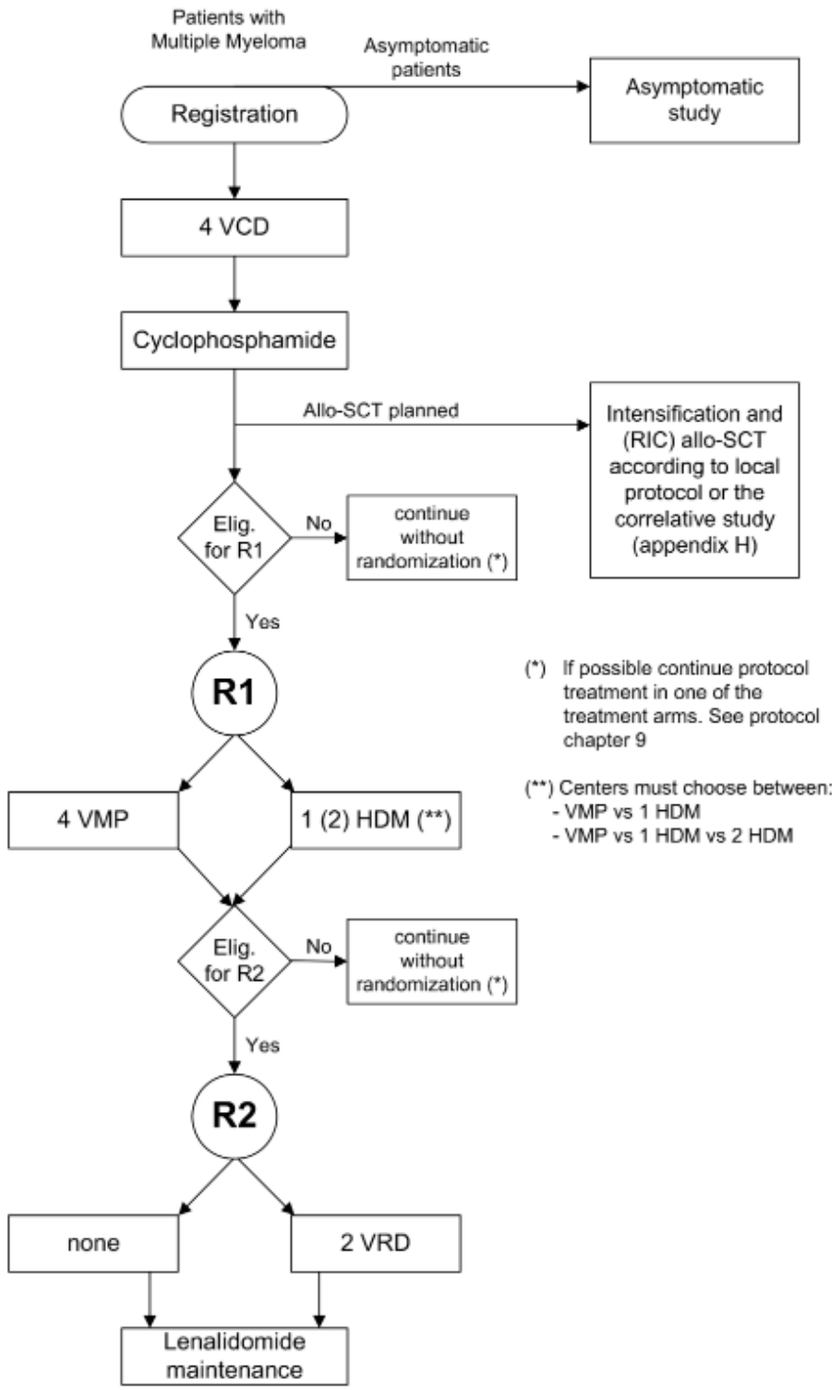
Diagnosi

- Diagnosi di MM IgG K (plasmacellule midollari 45%, , fish delezione 13q14' IgG 4542) nel maggio 2013
- ISS stadio II, ldh di norma
- Criteri crab multiple fratture patologiche colonna dorso lombare, aspetto tarlato della colonna in toto e ipercalcemia
- Arruolata in protocollo Hovon EMN02/H095 MM

Linee guida interne

- Prima scelta protocollo clinco
- In assenza di protocollo clinico induzione con 2-3 farmaci + doppio auto
- Se cariotipo avverso (high risk), paziente giovane e fit e ricerca donatore sibling hla id o mud 10/10. In tal caso auto+ allo
- Paz refrattario o recidiva precoce (sempre dopo il trapianto di cellule staminali autologhe) : ricerca donatore hla identico nella fratria e/ mud con minori restrizioni (8/8 o 7/8). Se risposta a tentativo di reinduzione trapianto allogenico

1 Scheme of study



(*) If possible continue protocol treatment in one of the treatment arms. See protocol chapter 9

(**) Centers must choose between:
- VMP vs 1 HDM
- VMP vs 1 HDM vs 2 HDM

Fase pre trapianto autologo I

- Dal 21/06/13 al 26/08/13 sommnistrati 4 VCD
- 18/09/13 somministrata ciclofosfamide mobilizzante 2 g/mq
- Somministrata 1 fl di plerixafor il 2.10 applicando il nostro algoritmo (17,56 cell micl = 0,13%) . Eseguite staminoafeersi i gg 3 e 4 /09/13 con raccolta complessiva di 5,6 x 10^6/kg cd34+(2 Sacche da 2.08 e 1 sacca da 1,5)

Biol Blood Marrow Transplant 20 (2014) 717–723

Peripheral Blood CD34+ Percentage at Hematological Recovery after Chemotherapy Is a Good Early Predictor of Harvest: A Single-Center Experience

Roberto Sorasio [1,*], Margherita Bonferroni [1], Mariella Grasso [1], Giuliana Strola [2], Davide Rapezzi [1], Dario Marenchino [3], Cristina Di Marco [1], Claudia Cas[illegible] [1], Daniele Mattei [1], Nicola Mordini [1], Francesca Fiore [1], Ivana Celeghini [1], Anna Borra [1], Annalisa Ghiglia [1], Andrea Gallamini [1,4]

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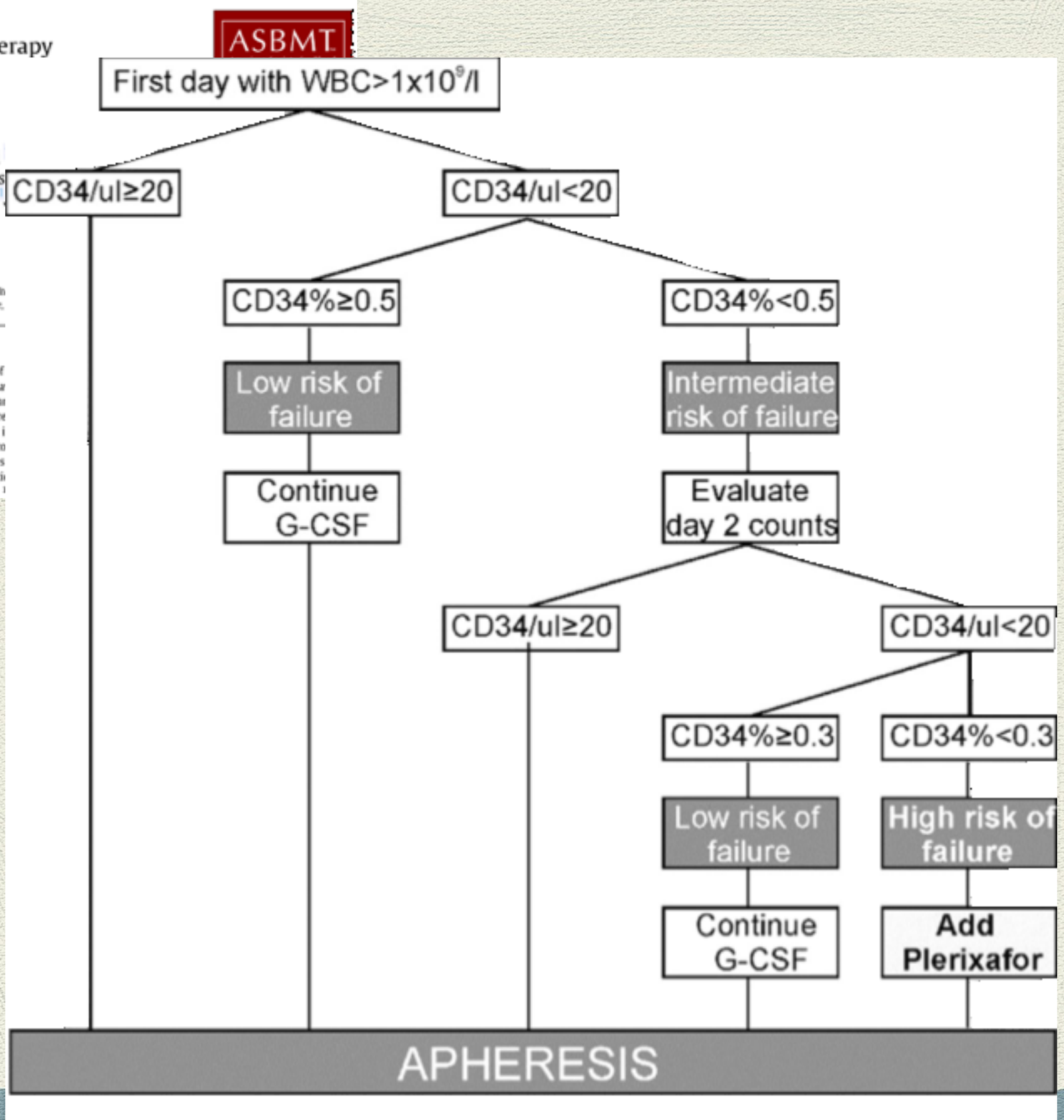
Mobilization failure
Plerixafor

A B S T R A C T

Several algorithms for early prediction of colony-stimulating factor administration ha[illegible] levels of CD34+ cells at a fixed day after sta[illegible] algorithm for early addition of plerixafor re[illegible] analyzed 280 chemomobilization attempts i[illegible] In multivariate analysis, CD34+ absolute co[illegible] (defined as the first day in which leukocytes[illegible] a total harvest ≥ 2 × 10^6 CD34+/kg. In pati[illegible]



Fase pre trapianto autologo II

- Paziente randomizzata nel braccio doppio autotrapianto
- Alla luce della politica interna di somministrare una dose di 4 -5 x10^6 kg cd34+ per ogni procedura autologa, si provvede ad un secondo tentativo di mobilizzazione con solo GCsf eventualmente associato a plerixafor on demand
- Sommnistrato plerixafor il 13.11, raccolte in data 14/11 4 x 10^6 kg cd34.

Stato pre trapianto autologo

- Rp 50% (IgG 2028)
- Valutazione midollare pre trapianto non eseguita (non richiesta dal protocollo)

Trapianto autologo

- 18 e19/11/2013 melphalan 100 mg/mq, reinfuse 2 sacche di staminali autologhe il 25 .11 (4,16 x 10 ^6 kg cd34+)
- Un addendum di staminali il 20.12 (1,5 x 10^6 kg cd34+) per persistente piastrinopenia con dipendenza trasfusiva.

Decorso post autotrapianto I

- Leucopenia persistente (dipendenza da Gcsf con 1/2 sommnistrazioni settimanali e piastrinopenia stabile intorno alle 20-30.000 x mm^3
- Esegue Biopsia ostomidollare il 19/1/2013 (+65) : cellularità del 50%, maturazione trilineare. Infiltrato plasmocellulare monoclonale k ammontante al 50% della cellularità totale
- Considerata non idonea al secondo trapianto autologo per citopenie persistenti in un quadro di modica risposta rispetto al pre trapianto (con tendenza all'incremento della CM da 1,4 g a 1,6 g; delle IgG da 1,68 a 1,883 g/L e del rapporto k\lambda da 14,380 a 19,700)

Decorso post autotrapianto II

- Fuoriuscita dal protocollo clinico
- Inizia lenalidomde (schedulati 4-6 mesi di terapia al dosaggio di 25 mg die per 21 giorni ogni 4 settimane) .
- Si attiva ricerca donatore non familiare (sorella hla diversa)
- Persiste leucopenia controllata dalla sommnistrazione di GCSF e piastrinopenia, intorno alle 20-30.000 x mm^3
- Riacutizzazioni ulcere arti inferiori

Essere strani non è un gran problema..Essere idioti.. Si!!

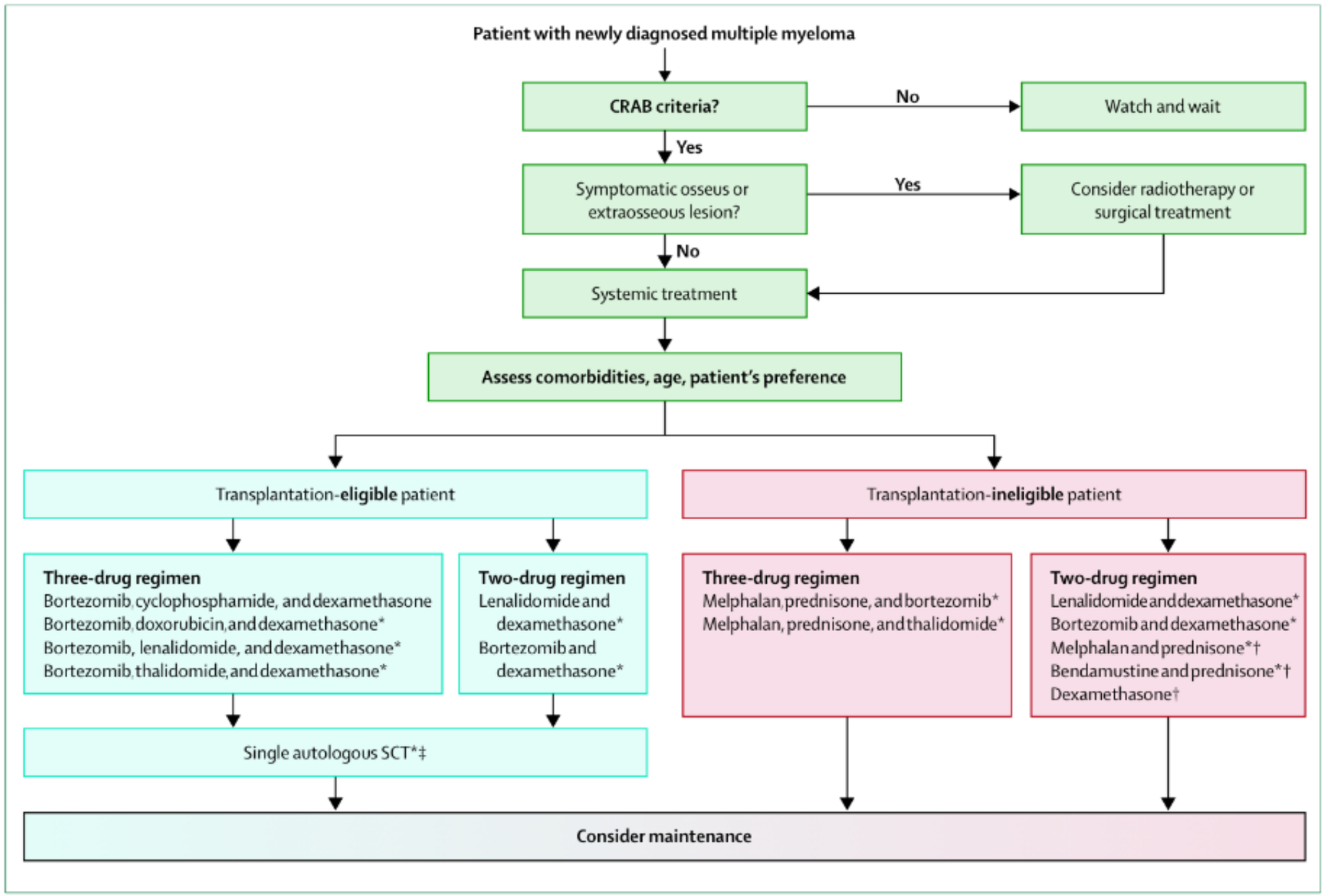


Figure 2: **Clinical management of patients with newly diagnosed multiple myeloma**
The listed therapy combinations are selected and not inclusive of all regimens. *Treatment combinations with evidence from randomised-controlled trials. †Melphalan + prednisone, bendamustine + prednisone, or dexamethasone can be used if novel drugs are not available or contraindicated. ‡Consider allogeneic stem-cell transplantation in young patients with deletion 17p and HLA-identical siblings.

C Rollig et al : Multiple Myeloma , Lancet 2015 May 30

Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org
ELSEVIER
ASBMT American Society for Blood and Marrow Transplantation

Guideline

Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation

Recommendations on the Role of Allo-HCT

Upfront myeloablative allo-HCT is not routinely recommended (grade A). It may be appropriate for further study in young patients with very high-risk MM, in the context of a clinical trial.

Planned RIC-allo-HCT after auto-HCT has not been found to be superior in the majority of clinical trials and is, therefore, not recommended over auto-HCT (grade A). Its role in high-risk subgroups requires further study.

Allo-HCT salvage therapy for relapsed MM has not been shown to be superior to salvage auto-HCT and is not routinely recommended outside of a clinical trial (grade D). For younger patients with a good performance status, allo-HCT can be considered, ideally in the context of a clinical trial.

The role and choice maintenance after allo-HCT has not been adequately studied and is not known.

American Society of Blood and Marrow Transplant, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma

S GIRALT ET AL , BBMT 2015

Consensus Guidelines Regarding Role of Allogeneic HCT in Relapsed Myeloma

The expert committee agreed on the following guideline statements:

1. Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT or with high risk features (i.e cytogenetics, extramedullary disease, plasma cell leukemia or high LDH) provided that they responded favorably to salvage therapy before allogeneic HCT.

2. Whenever possible allogeneic HCT should be performed in the context of a clinical trial.
3. The role of post allogeneic HCT maintenance therapy needs to be further explored.
4. Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy.

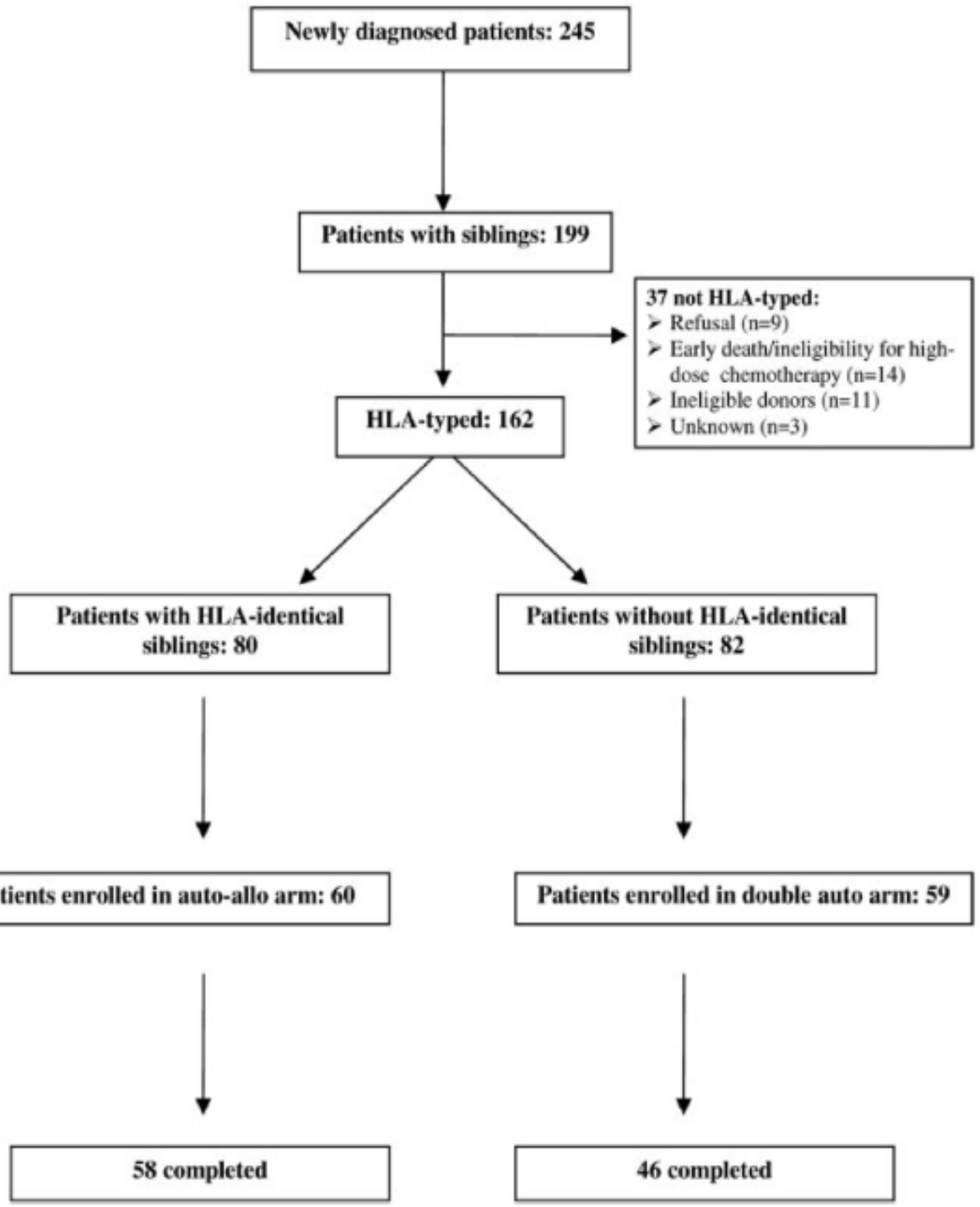
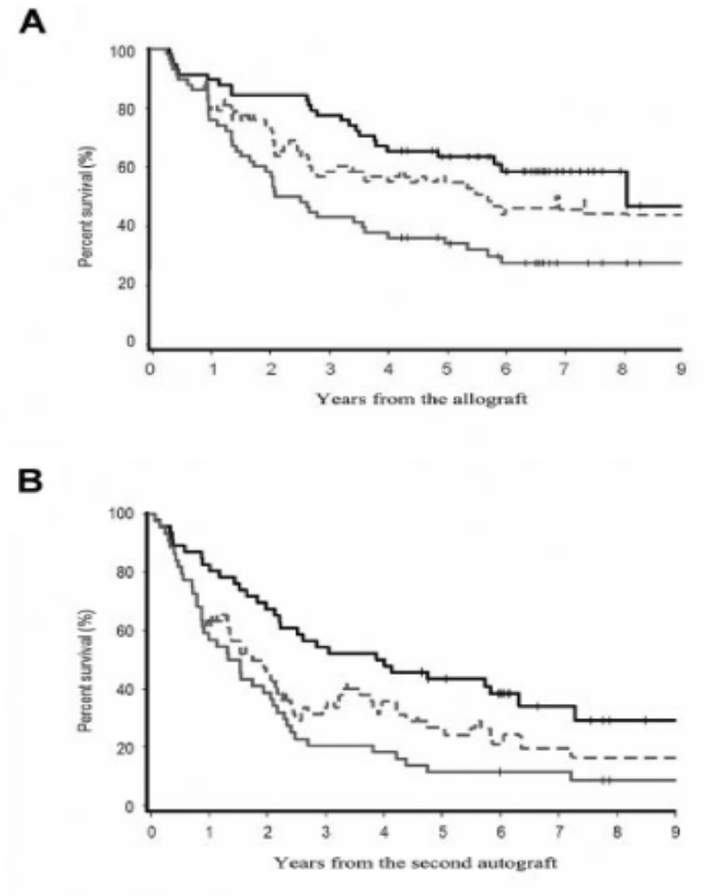


Figure 1. CONSORT diagram.



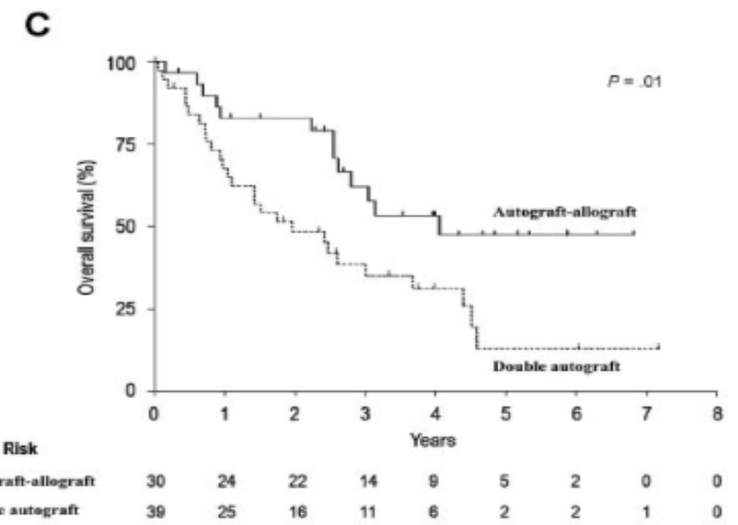


Figure 3. Survival after salvage treatment. Probabilities of a patient being alive in the original complete (CR) or partial remission (PR) or in a subsequent remission because of salvage therapy after the nonmyeloablative allograft (A) or the second autograft (B) calculated by the Couper method (dotted line). Black and gray solid lines represent overall (OS) and event-free survival (EFS) by the Kaplan-Meier methods (see "Long-term clinical outcomes"). (C) OS, calculated from first relapse, of patients who relapsed after the nonmyeloablative allograft (solid line) and after the second high-dose melphalan autograft (dotted line).

Risposta alla recidiva post trapianto

HM Lokhorst et al, Haematologica 2015

Reduced relapse rate in upfront tandem autologous/reduced-intensity allogeneic transplantation in multiple myeloma only results in borderline non-significant prolongation of progression-free but not overall survival

LETTERS TO THE EDITOR

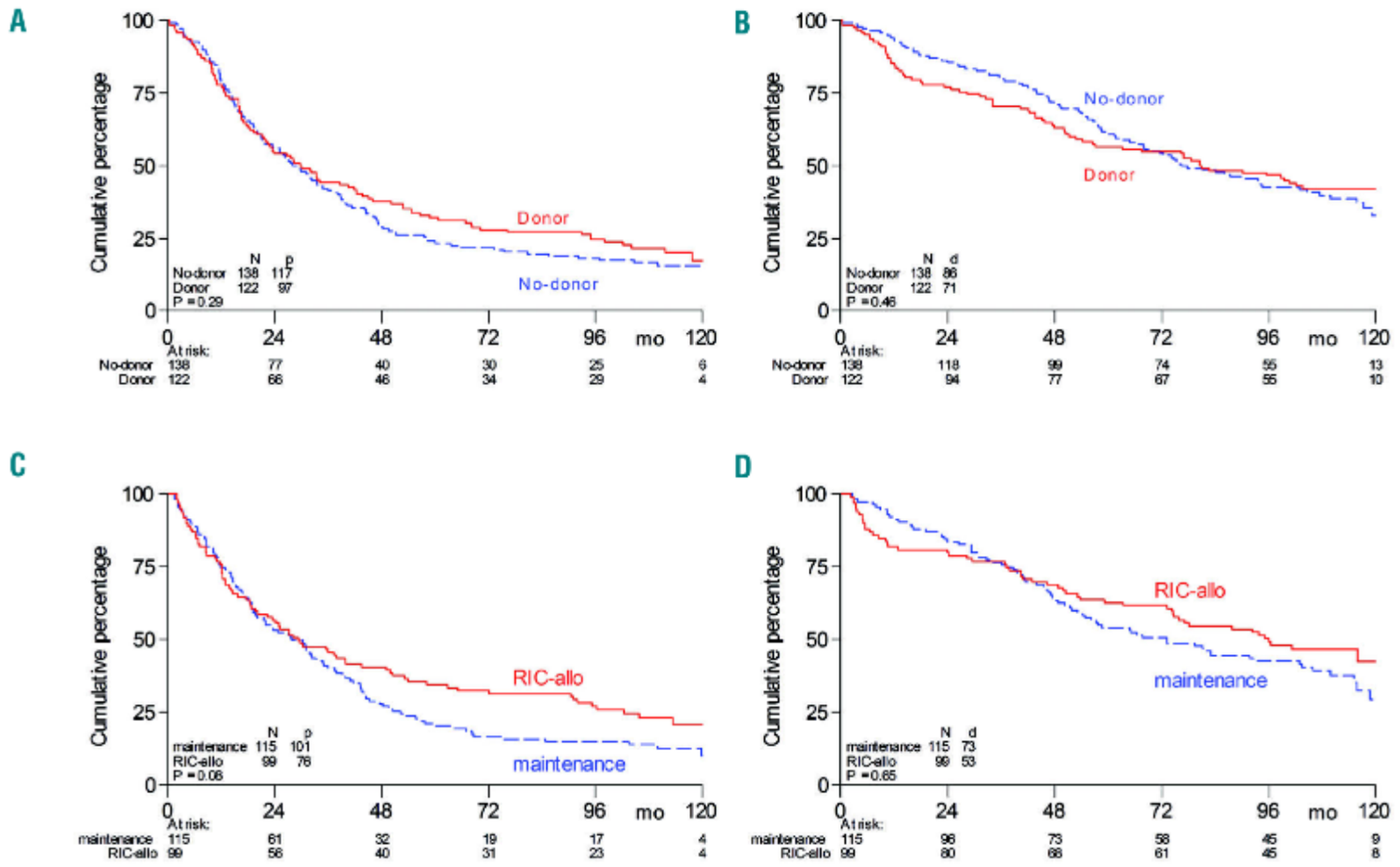


Figure 2. Kaplan-Meier survival curves. Actuarial rates of PFS (A) and OS (B) according to availability of an HLA-identical sibling of patients included in the HOVON-50 study. PFS and OS are presented as from the date of autologous SCT. Actuarial rates of PFStr (C) and OStr (D) according to treatment started after Auto-SCT, ie, Allo-SCT *versus* maintenance with thalidomide or α-interferon. PFStr and OStr are presented as from the date of Allo-SCT or start of maintenance, whichever was applicable. The reported *P* values are those obtained with the RMST method.

Leukemia 2015

LETTER TO THE EDITOR

Prospective molecular monitoring of minimal residual disease after non-myeloablative allografting in newly diagnosed multiple myeloma

M Ladetto[1,2,3], S Ferrero[1,2], D Drandi[1,2], M Festuccia[1,2], F Patriarca[4], N Mordini[5], S Cena[1], R Benedetto[1,2], G Guarona[1,2], F Ferrando[1], L Brunello[1,2], P Ghione[1,2], V Boccasavia[1], R Fanin[4],

npg

Graft-vs-myeloma after non-myeloablative allografting determined prolonged rates of MR similar to those described after myeloablative allografting and higher than those recently reported after a planned treatment combination of an autograft with VTD consolidation.[10] In the light of our and of others results, it may become ethical to evaluate in newly designed clinical trials the combination of graft-vs-myeloma with novel agents in young high-risk and/or early relapsed patients where life expectancy is poor also in the era of new drugs.

Multiple Myeloma: EBMT/GITMO-Data

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
GITMO ITALY		81	115	128	129	103	94	94	70	86	85	71	86	55	73
MIS APLO												1	12	4	10
EBMT ALLO	393	405	523	573	594	565	494	498	525	567	614	601	668	606	
EBMT AUTO	3520	4283	4843	5487	5926	6374	6564	6743	6833	6874	7260	8586	9214	9794	

Cortesia B Bruno

European Myeloma Network trial phase II: Current status (october 2015)

Spain: 7 patients included - Italy: 2 patients included

Phase I			
ID	Disease status at transplant	Response to transplant	Relapse
01-05	PR (4 prior lines)	PR	NO
05-01	VGPR (3 prior lines)	N/E	NO
01-06	VGPR (2 prior lines)	RC (MRD-)	NO
01-07	VGPR (2 prior lines)	RC (MRD-)	NO
10-01	PR (2 prior lines)	N/E	
16-01	SD (2 prior lines)	RC (MRD-)	NO

Cortesia B Bruno

Paziente sintesi clinica

- Paziente con ridotta riserva midollare
- Persistentemente citopenica
- Buona Rp migliorata con lenalidomide ma raggiunto plateu
- Ulcere ricorrenti arti inferiori
- Identificato donatore mud 10/10

Caratteristiche triapianto allogenico

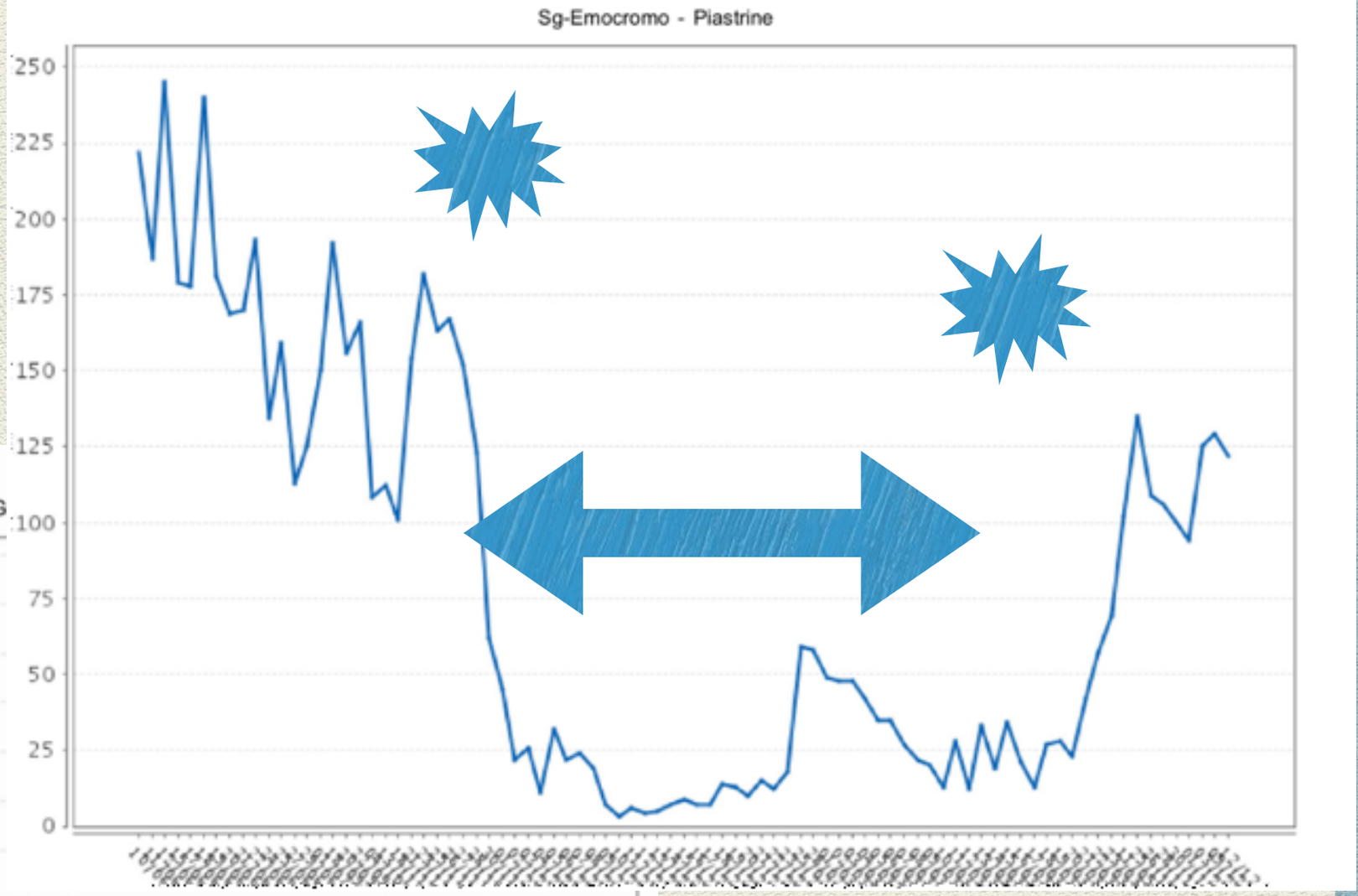
- Registro estero
- Maschio , 40 anni, gruppo AB pos vs O pos (titolo del pazeinte anti A IgG 2 e IgM 1 , anti B IgG 2 e IgM 1), CMV neg vs pos
- Regime di condizionamento Bu flu ridotto (3 giorni di Busulfano)
- Profilassi gvhs : cs + mmf+ ATG (Thymo) 5 mg /kg

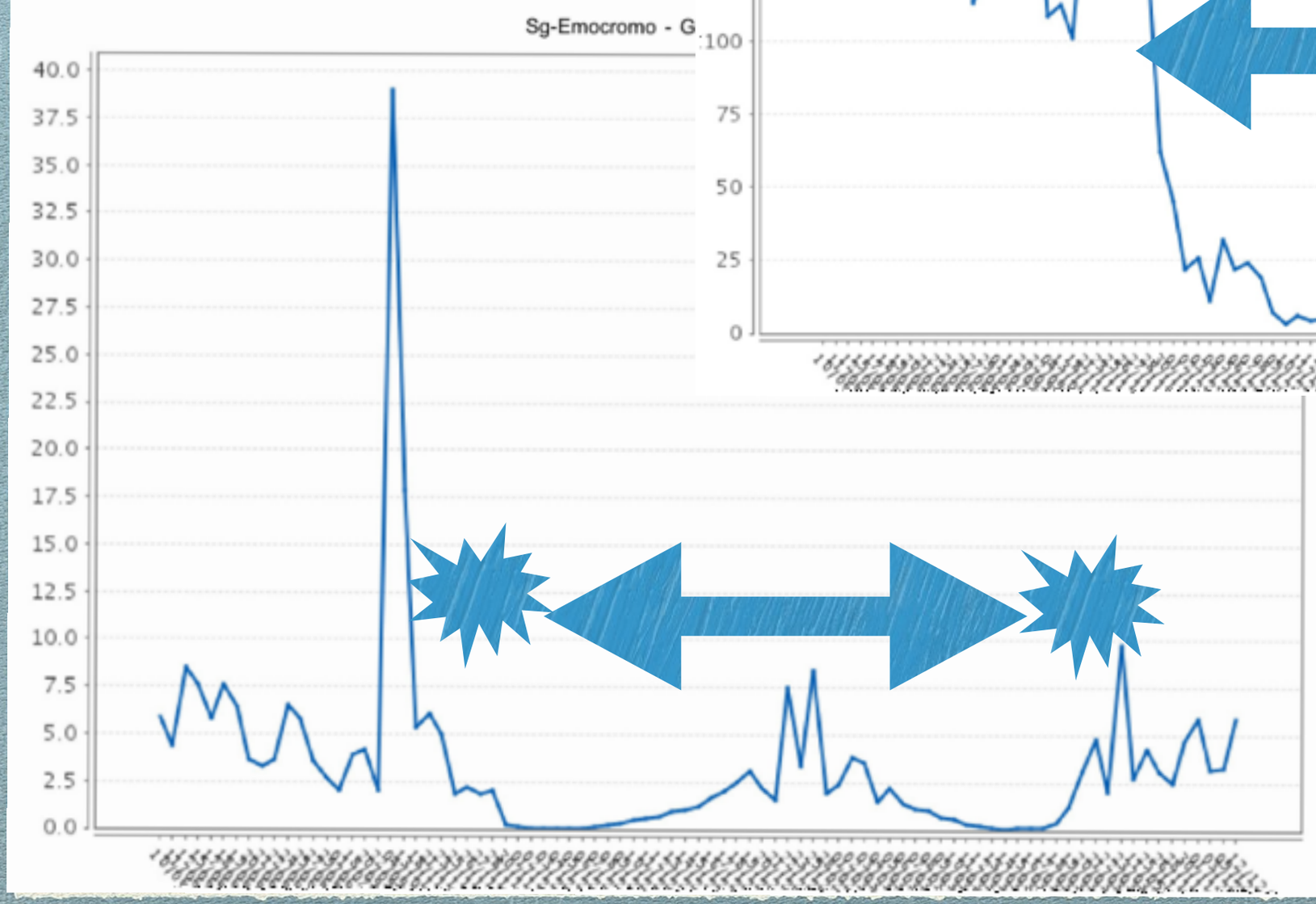
Caratteristiche trapianto allogenico II

- Fonte cellule staminali: midollo osseo
- Infuse il 4/3/14 1,64 X 10^8/kg mononucleate , 1,27 x10^6/kg cd34+, contaminata da cocchi
- Take dei neutrofili + 15
- Take delle piastrine +20 > 30.000X mm^3, +22> 100.000
- Complicanze : mucosite II grado

Decorso alloBMT

- +90 GvHD grado II (sindrome del tratto gastoenterico superiore) e contemporaneamente positivizzazione EBV DNA (sommnsitrata una dose di rituximab ev) e risttivazione cmv .
- Gvhd cronica moderata riacutizzata dopo sospensione terapia IS (attualmente basse dosi , 10 mg die e bassa dosi di ciclosporima 50 mg die)
- Dicembre 2015 ricovero per ulcera AAII infettata da Pssudomonas sensibile a colestina e Staf mrsa


Sg-Emocromo - Piastrine
250
225
200
175
150
125
100
75
50
25
0


Sg-Emocromo - G
40.0
37.5
35.0
32.5
30.0
27.5
25.0
22.5
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
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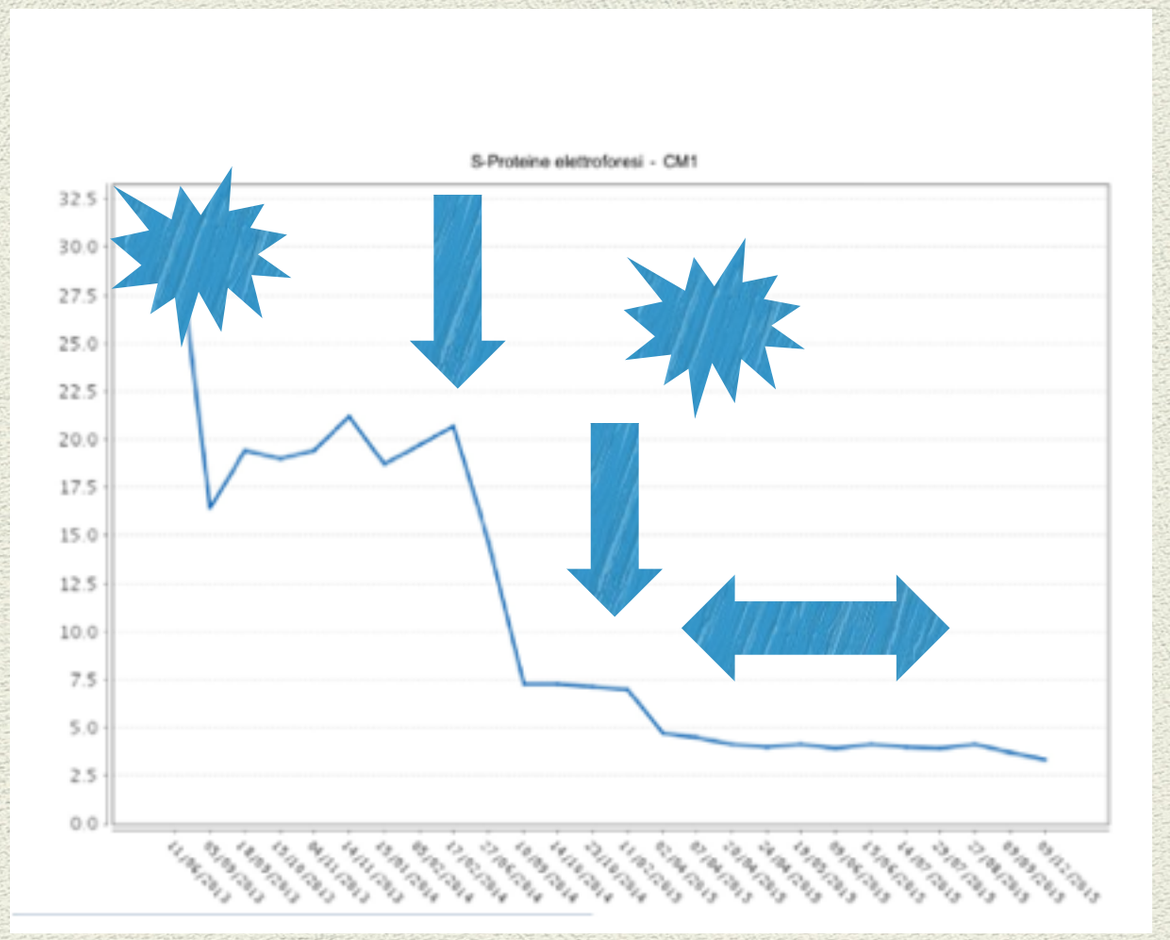
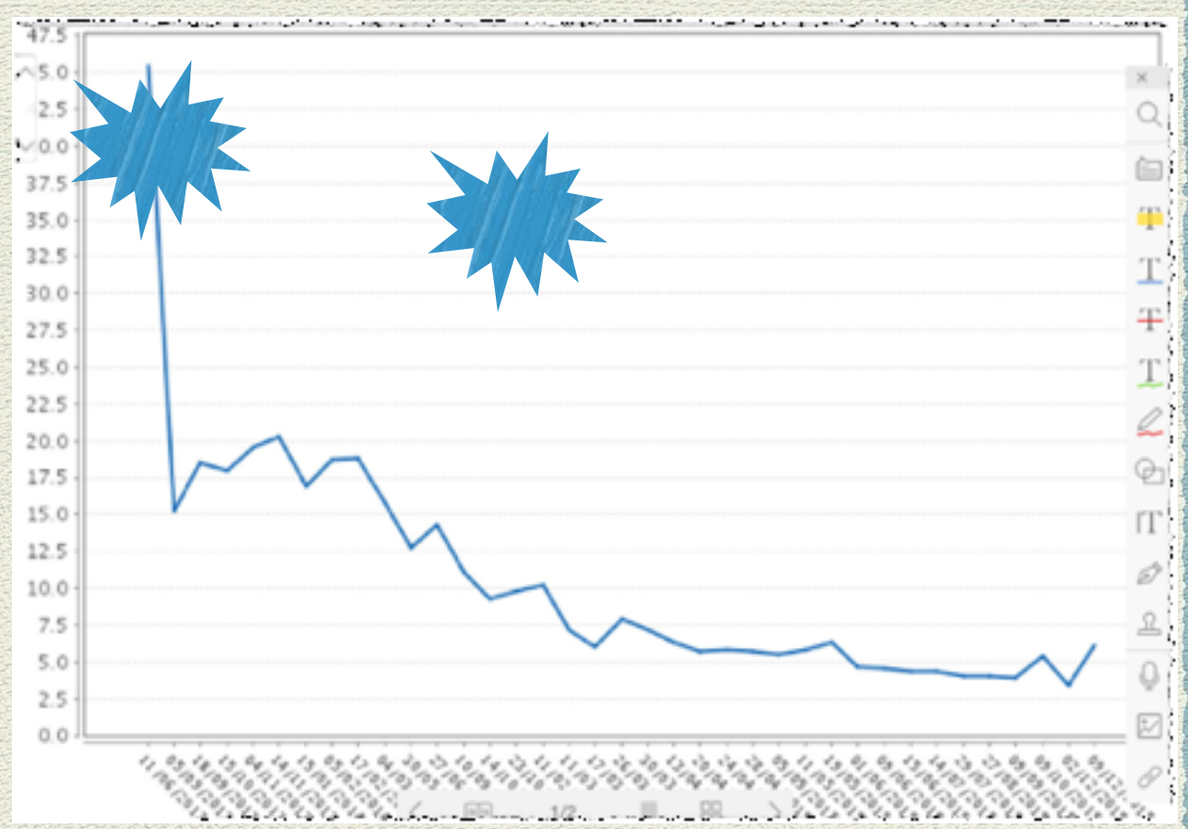
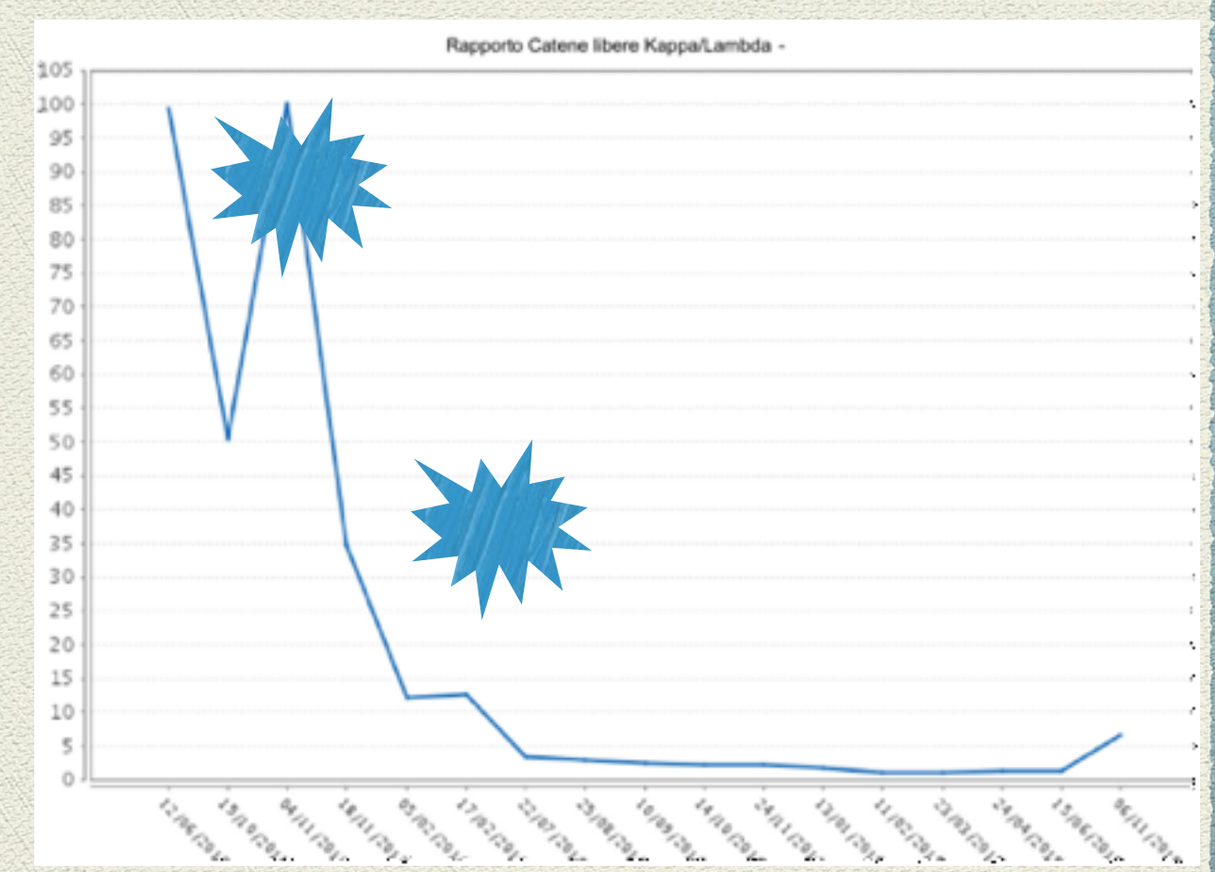

S-Proteine elettroforesi - CM1




Rapporto Catene libere Kappa/Lambda -


A questo punto della mia vita ho deciso di guardare sempre avanti!
No, non è saggezza... E che se mi giro troppo all'indietro mi fa male la cervicale.

Riflessioni I

- L’associazione nuovi farmaci /trapianto di cellule staminali allogeniche puo’ essere una terapia molto (l’unica ?) efficace in pazienti selezionati (alto rischio clinico)

- Invito molto chiaro dalla letteratura per l’esplorazione del trapianto allogenico nel setting del mieloma giovane ad alto rischio

- Tutti dati di studi clinici con follow up lunghi (8-10 anni) non vedono il braccio del trapianto allogenico (ridotta intensita’) inferiore al braccio autologo

Riflessioni II

- I dati di tossicita' relativi al trapianto allogenico con regime convenzionale sono relativi ad un'altra era trapiantologica . Oggi abbiamo a disposizione:

  - Nuovi regimi convenzionali a tossocita' ridotta (Bu Flu)

  - Migliori informazioni sui metodi di prevenzione della GvHD acuta e cronica

  - Migliori conoscenze sulla diagnosi e terapia delle malattie infettive (es problematica fungina)

GRAZIE PER L'ATTENZIONE