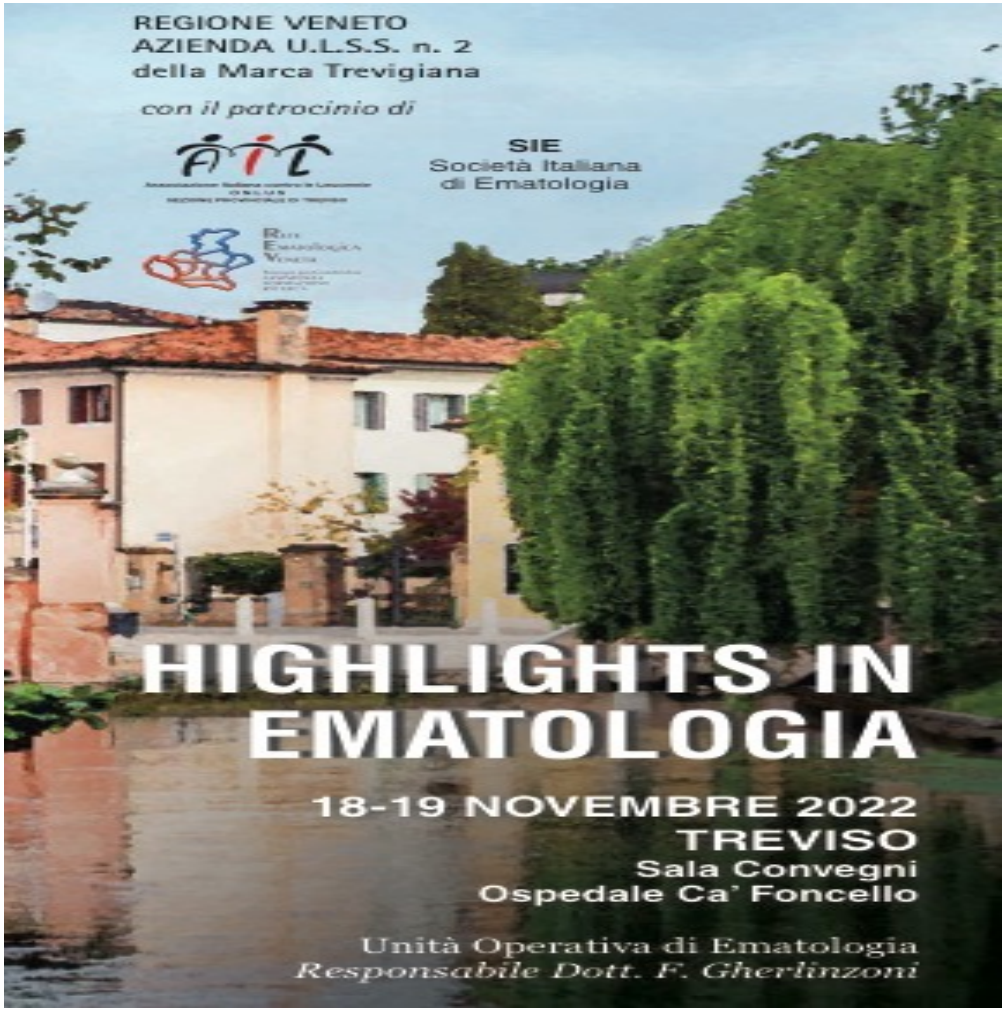


SESSIONE IV
TRAPIANTO DI MIDOLLO OSSEO ALLOGENICO

Le patologie a lungo termine dei pazienti trapiantati

renato.fanin@uniud.it

EBMT European Society for Blood and Marrow Transplantation

Introduction

Delayed complications

Late complications

Very late complications

Screening for complications

Symptoms & syndromes/quality of life

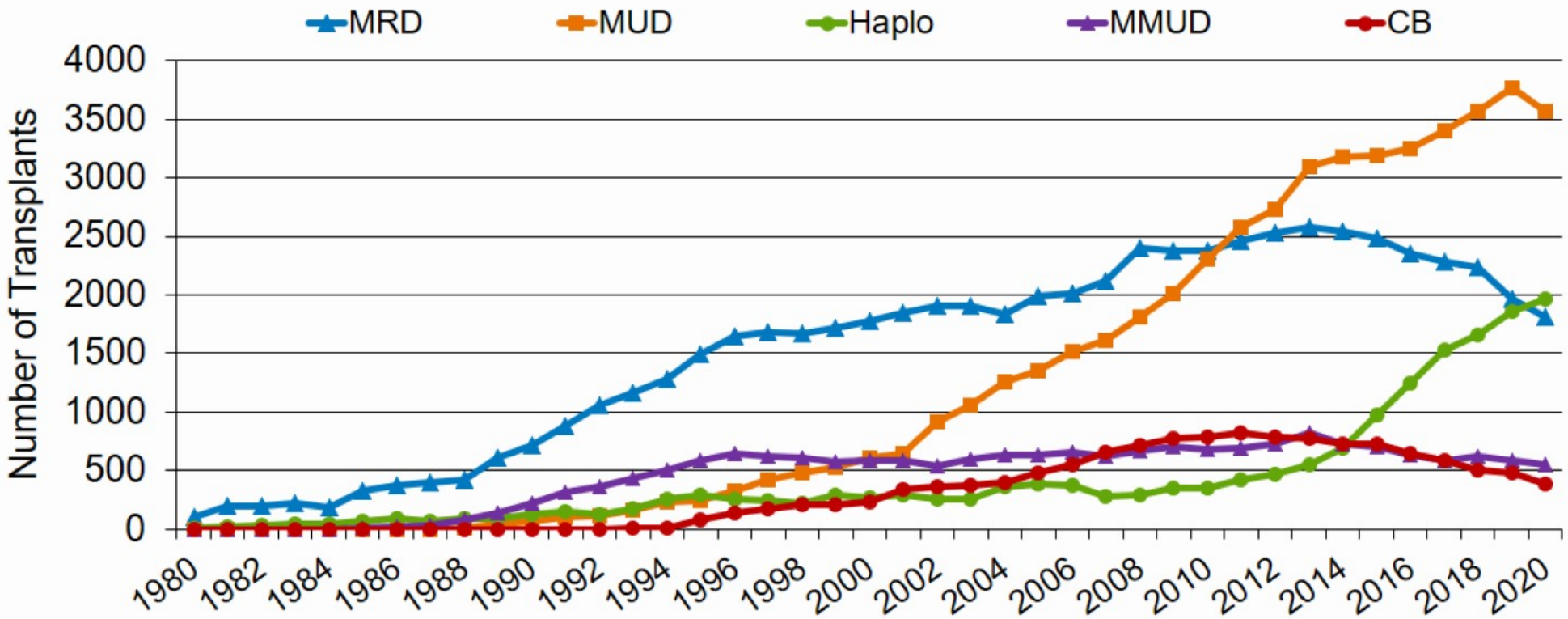
Interventions for improvement of QOL

Conclusions

Introduction - General consideration(1)

- **Transplant activity** has steadily increased over time with introduction of safer regimens, newer indications, and alternative graft sources .
- With improvements in supportive care **long-term survivors** following allogeneic transplantations have increased.
- As a result, the number of patients living with **long-term toxic effects** due to HSCT has increased.

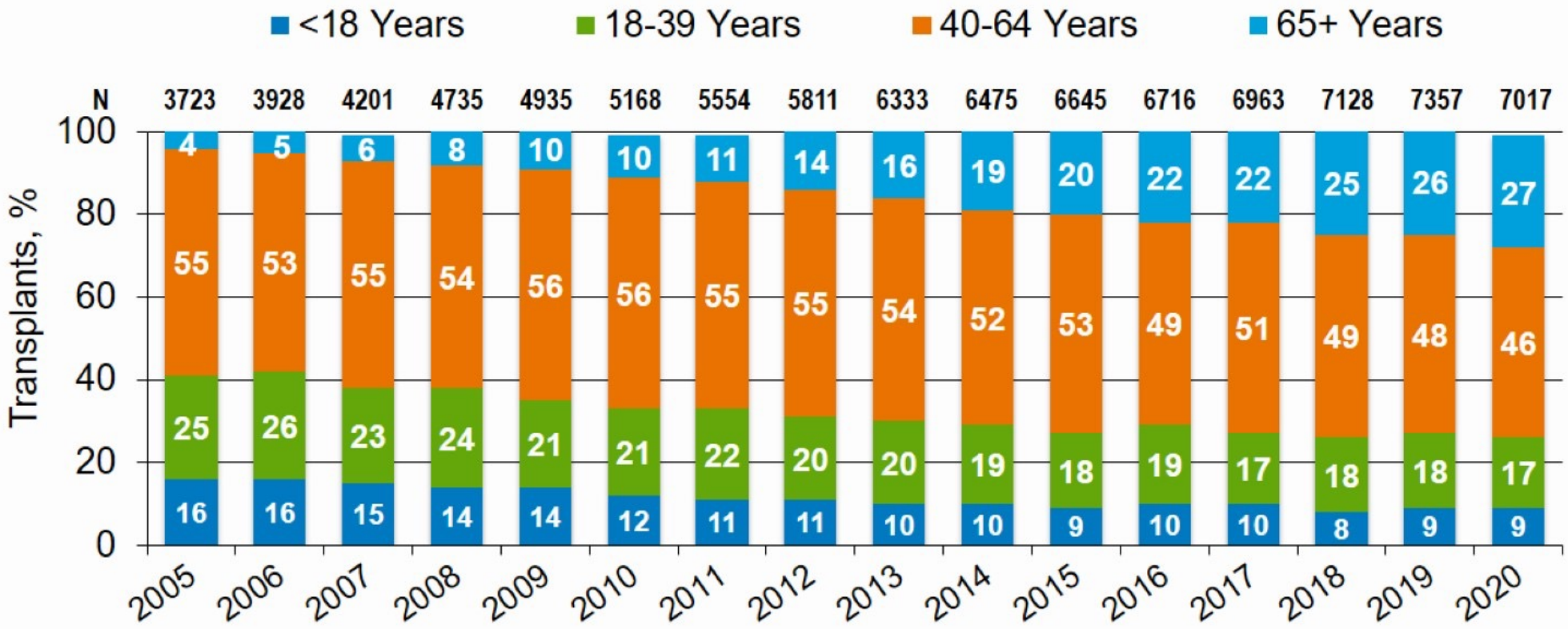
Number of Allogeneic HCTs in the US by Donor Type



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

Relative Proportion of Allogeneic HCTs for Malignant Diseases* in the US by Recipient Age



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*includes Acute myelogenous leukemia, Acute lymphoblastic leukemia, Myelodysplastic syndromes/Myeloproliferative neoplasms, Non-Hodgkin lymphoma, Hodgkin lymphoma

HOW TO KNOW THE PREVALENCE OF HCT SURVIVORS ?

Simulation model National Marrow Donor Program

Increasing HCT survivors

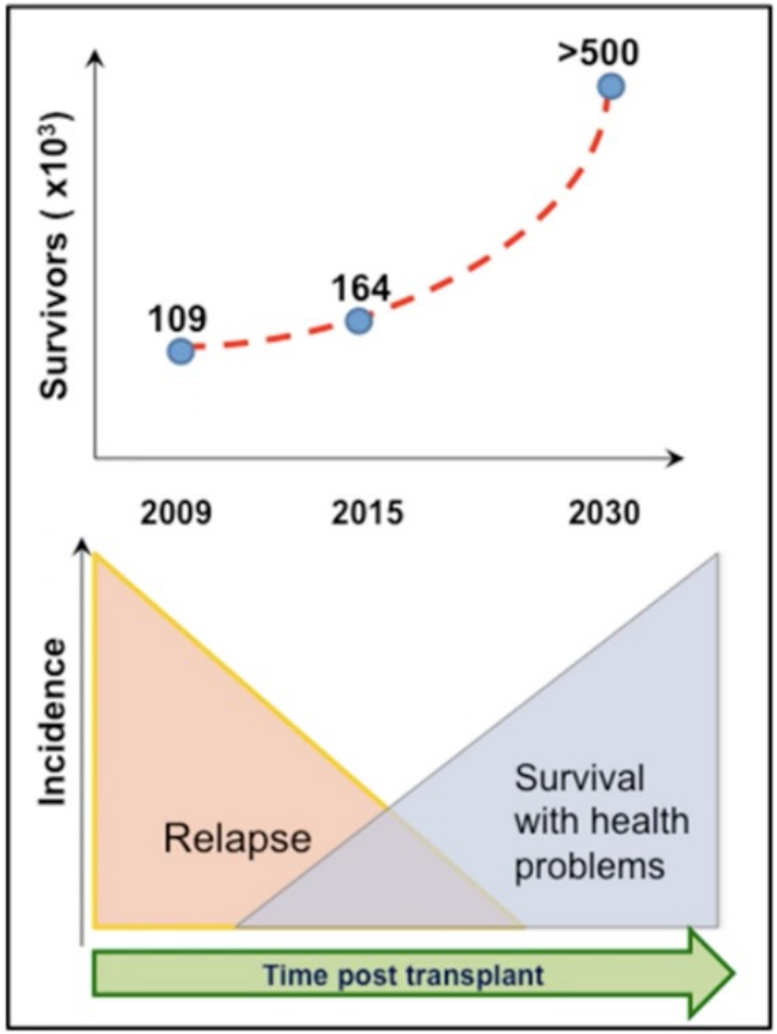
More transplants

CIBMTR data
170.628 Pts. transplanted
1968-2009

New focus on long term survivorship

2020: >250, 000
2030: >500, 000

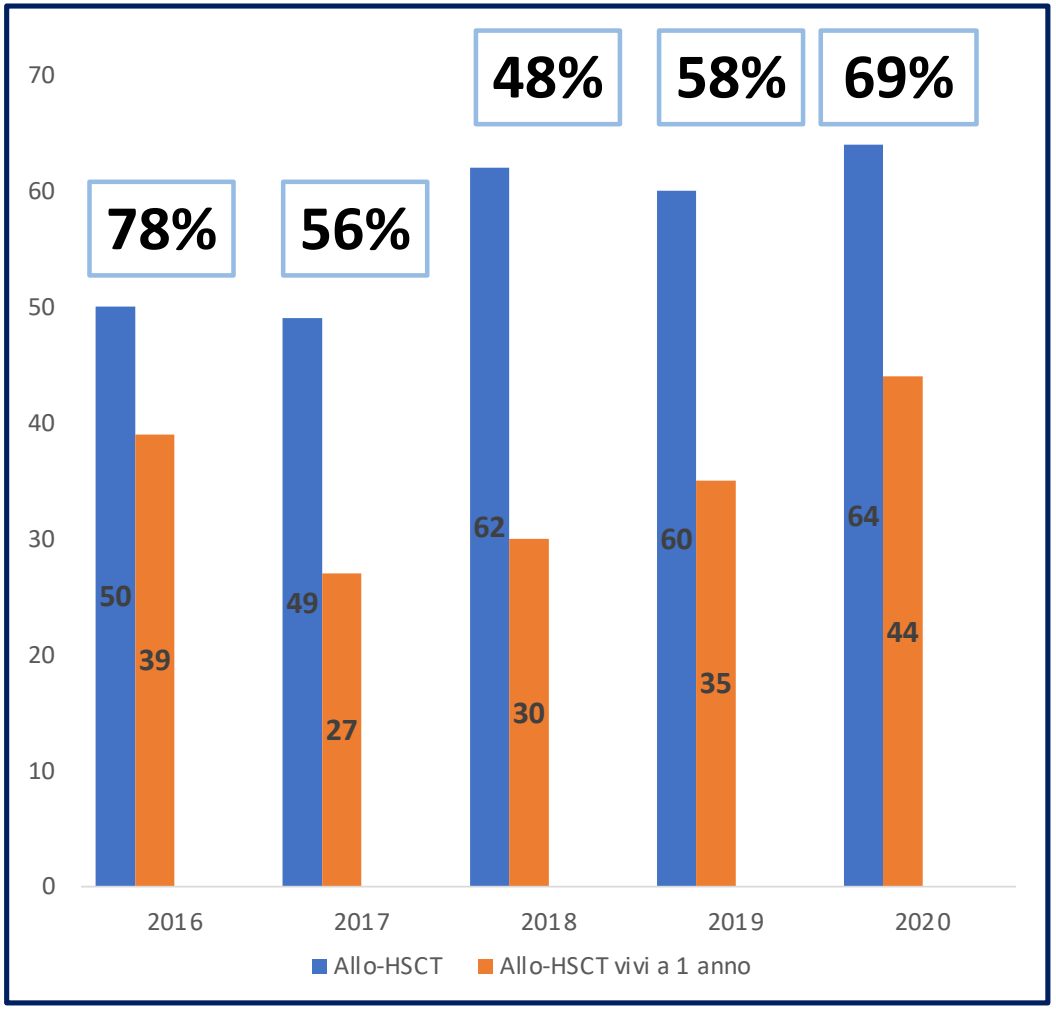
60% auto HCT; 40% allogeneic HCT
60% aged 18-59

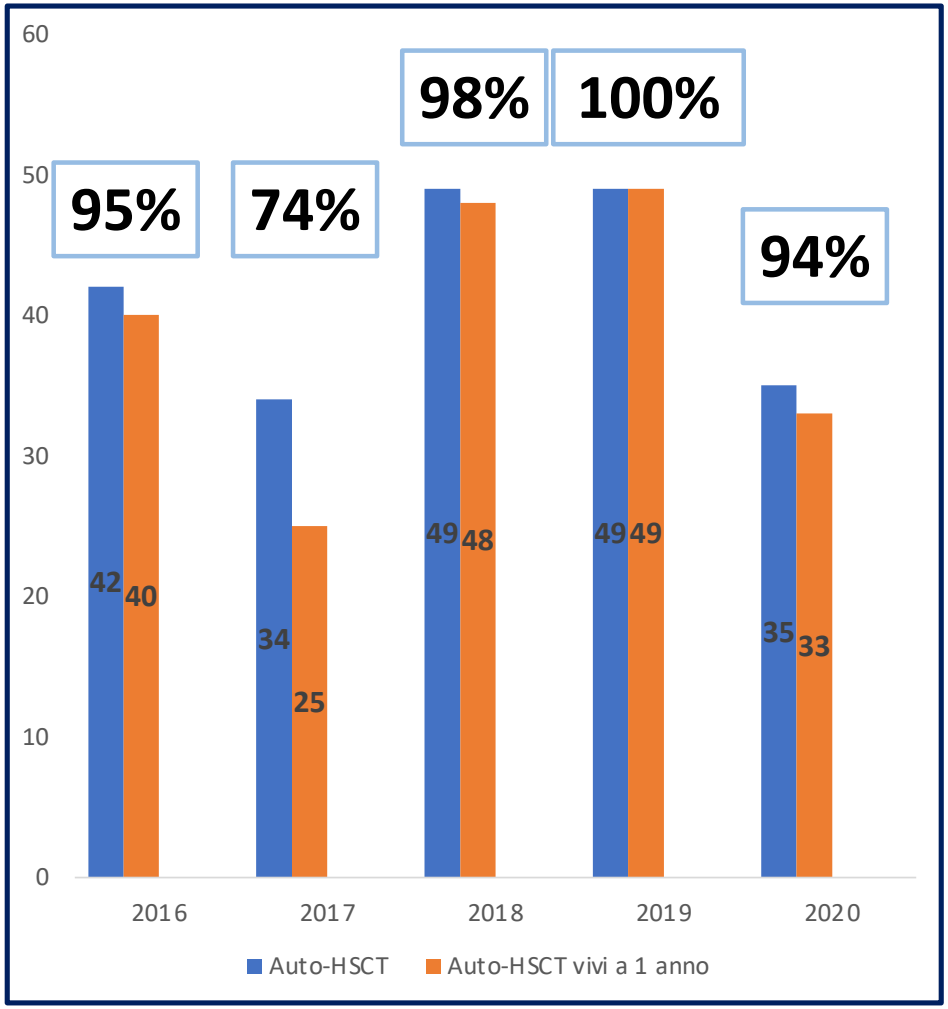


Majhail et al.Biol Blood Marrow Transplant. 2013 Oct;19(10):1498-501

Battiwalla M. BMTinfonet.org survivorship symposium. 2022

Allo-HSCT and Auto-HSCT – Udine Experience – 1 Year survivors

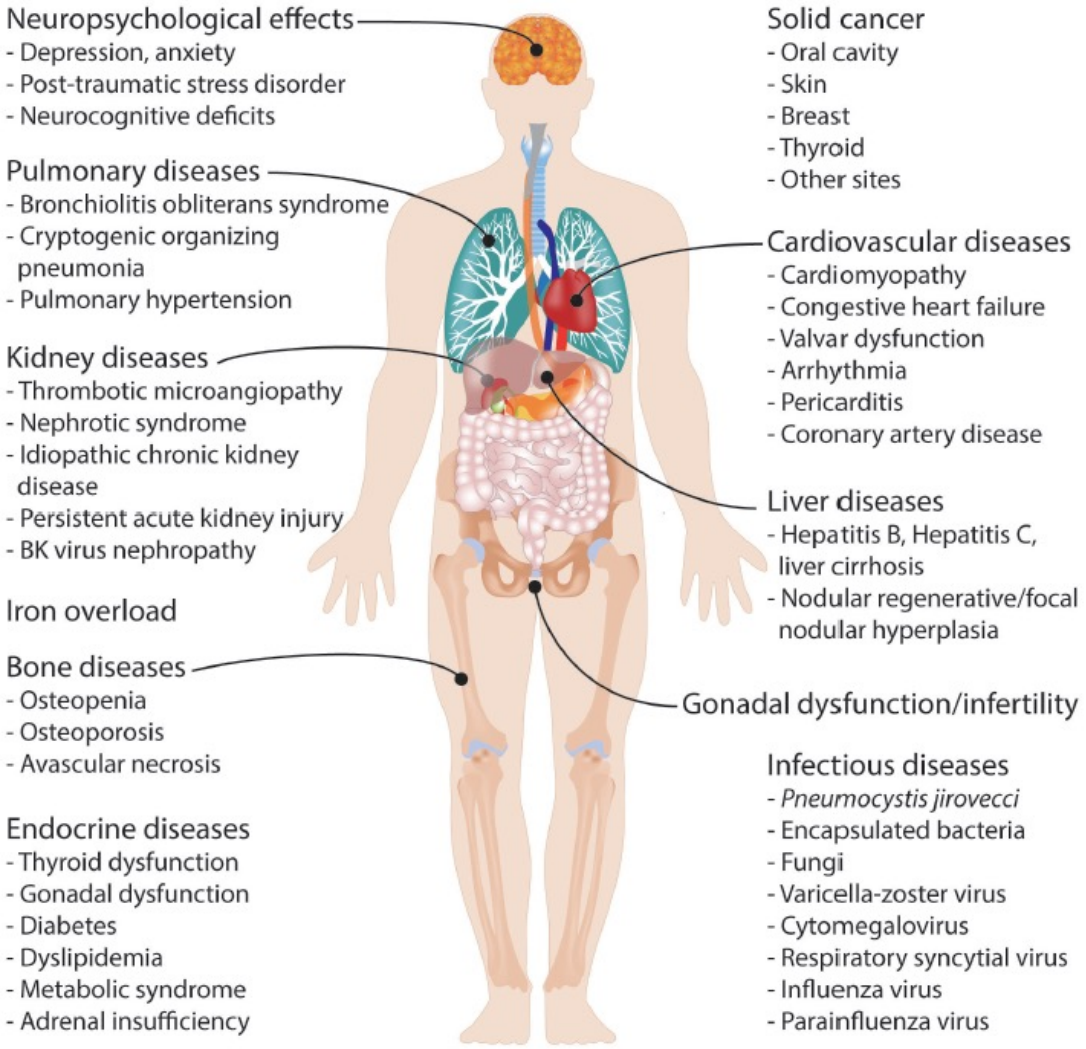




Introduction - General consideration (2)

- Patients who survive in remission for the first few years after transplantation have an 80% to 90% **probability of surviving** over the following 10 to 15 years ,but **life expectancy** remain 30% lower compared with the general population
- However, these survivors continue to experience increased **morbidity and mortality** from late complications related to pre-, peri-, and post-transplant treatment exposures and need lifelong surveillance for their screening and prevention

Late Effects of Hematopoietic Stem Cell Transplantation



Inamoto Y et al, Haematologica, 2017

Late Effects of Hematopoietic Stem Cell Transplantation

Table 1. Late effects after blood and marrow transplantation

Late effect	Incidence	Mortality	Morbidity	Treatable	Preventable
Cardiovascular	+	+	+	+	+
Pulmonary					
Bronchiolitis obliterans syndrome	+	++	++	+	-
Cryptogenic organizing pneumonia	+	+	+	++	-
Pulmonary hypertension	+	++	++	+	-
Endocrine					
Thyroid dysfunction	++	-	-/+	+++	-
Diabetes	++	+	+	+++	-
Dyslipidemia	++	-	-/+	+++	-
Adrenal insufficiency	+	-	-/+	+++	-/+
Gonadal dysfunction/ infertility	+++	-	-	-/+	-/+
Iron overload	++	-	-	++	-
Liver					
Hepatitis B	+	-	+	++	+
Hepatitis C and cirrhosis	+	-	+	++	-/+
Nodular regenerative hyperplasia	+	-	-	-	-
Focal nodular hyperplasia	+	-	-	-	-
Kidney					
Thrombotic microangiopathy	+	+	++	-/+	-
Nephrotic syndrome	+	-	++	++	-
Idiopathic chronic kidney disease	+	-	++	+	-
Bone					
Osteoporosis/osteopenia	++	-	-	++	+
Avascular necrosis	+	-	++	++	-
Infection	++	+	+	+++	+
Solid cancer	+	++	+++	-/+	-
Neuropsychological	++	-	++	+	-
Recurrent disease	++	+++	+++	-/+	-
Chronic graft-*versus*-host disease	++	+	++	+	

+ : <20%; ++ : 20%-50%; +++ : >50%.

Inamoto Y et al, Haematologica, 2017

LATE EFFECTS:
Point of view of physicians and patients

- Quality of life
- Fertility
- Social rehabilitation
- Work reintegration

The leading causes of excess deaths in 5-year survivors included : secondary malignancies (27%), recurrent disease (14%), infections (12%), chronic GvHD (11%), cardiovascular diseases (11%), and respiratory diseases (7%)

Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study

Can-Lan Sun,[1] Liton Francisco,[1] Toana Kawashima,[2] Wendy Leisenring,[2] Leslie L. Robison,[3] K. Scott Baker,[2] Daniel J. Weisdorf,[4] Stephen J. Forman,[5] and Smita Bhatia[1]

HCT at City of Hope National Medical Center (COH) or the University of Minnesota between 1974 and 1998

Eligible Criteria

- HCT for a hematologic malignancy or severe aplastic anemia, survived at least 2 years after transplantation
- Alive and 18 years of age or older at study participation

2175,AUTO,ALLO,74-98,1663 alive at 2 ys

1022 patients → **309 sibling**

Chronic Conditions (CC)

- **≥ 1 CC: 66%**
- ≥ 2 CC: 50%
- ≥ 3 CC: 34%
- 2x risk (95% CI, 1.6-2.1) compared to sibling

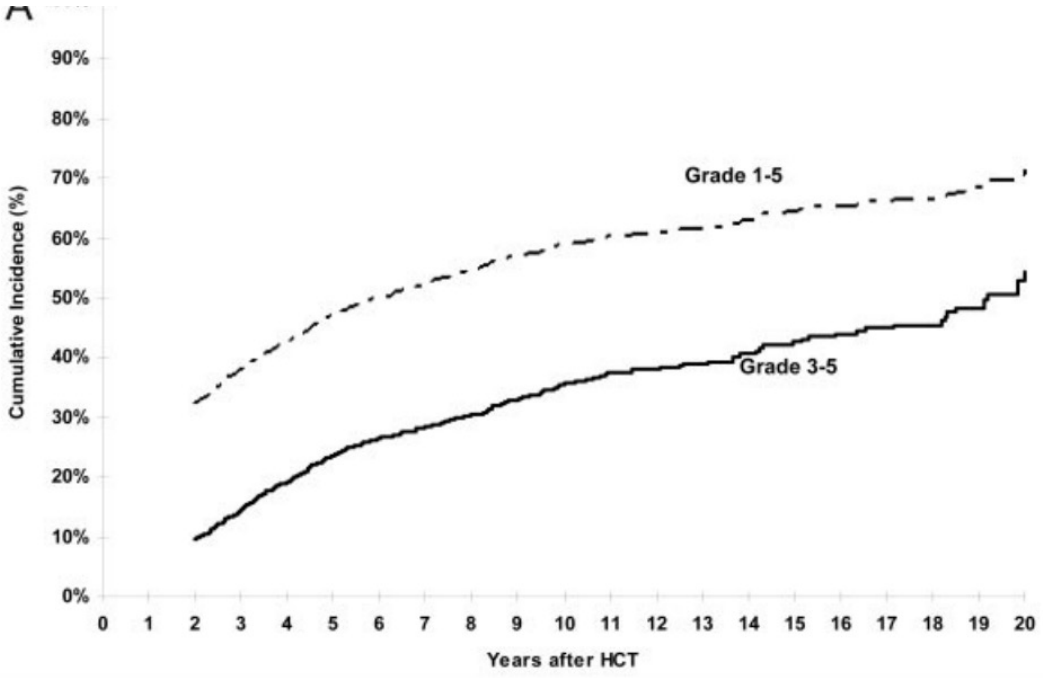
Severe/Life-threatening conditions

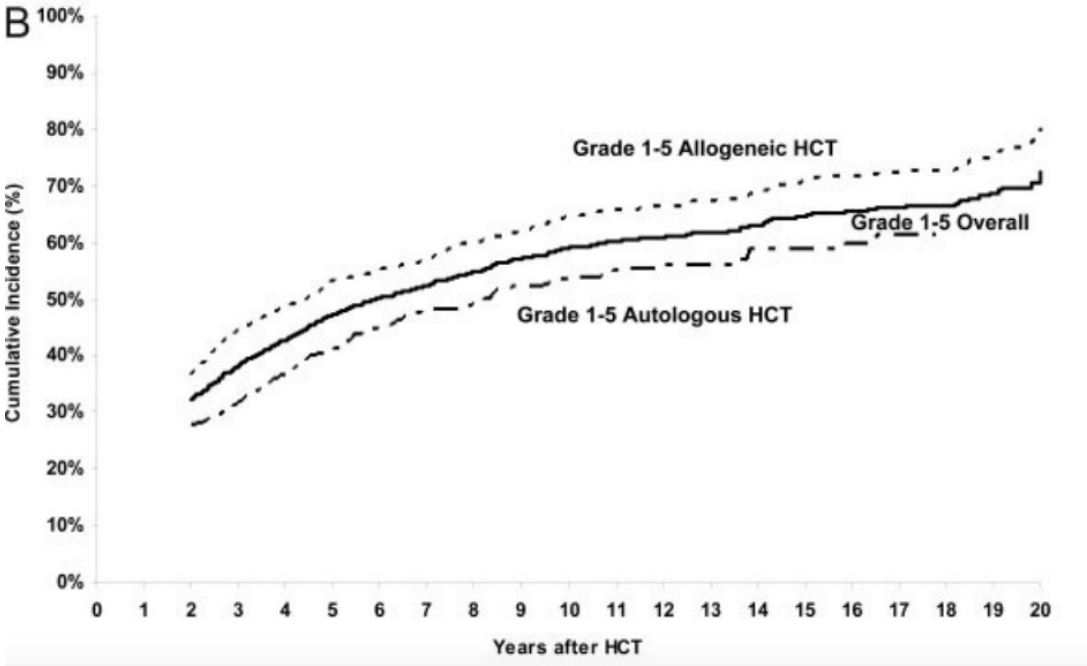
- **18% of patients**
- 3.5x risk (95% CI, 2.3-5.4) compared to sibling

Sun CL et al, Blood. 2010

10-year cumulative incidence for chronic conditions: 59%

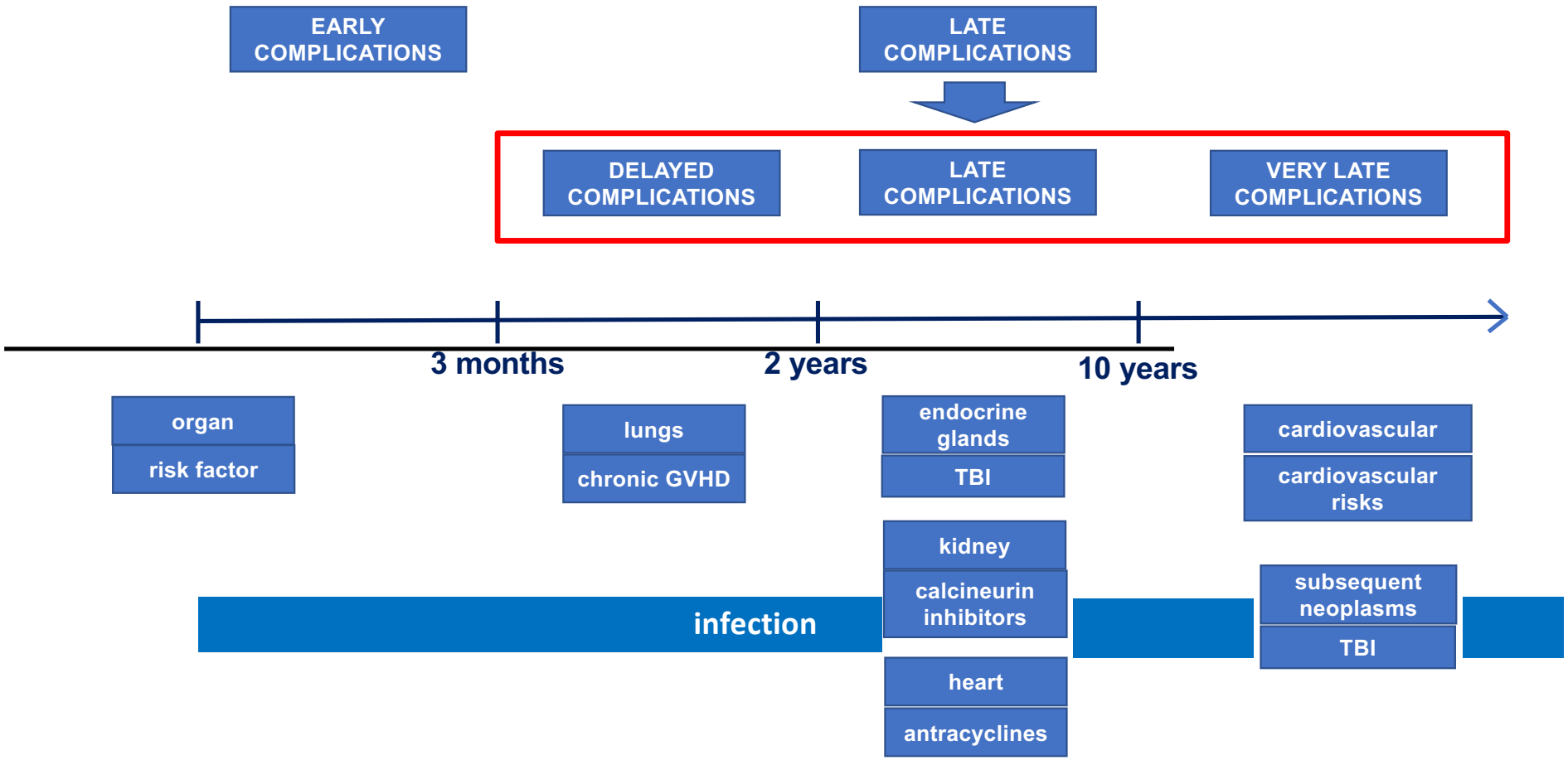
10-year cumulative incidence for Severe/Life-threatening conditions: 35%





Sun CL et al, Blood. 2010

Introduction
Complications after HSCT



EBMT European Society for Blood and Marrow Transplantation

Introduction

Delayed complications (3mos - 2 ys)

Late complications

Very late complications

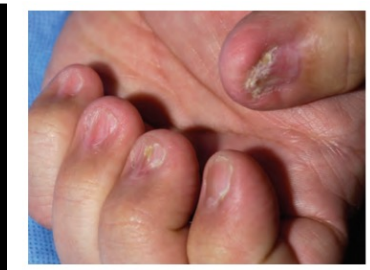
Screening for complications

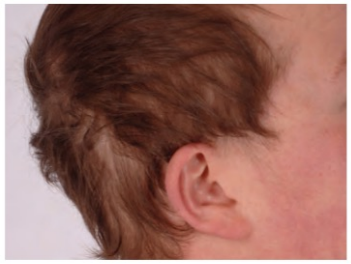
Symptoms & syndromes/quality of life

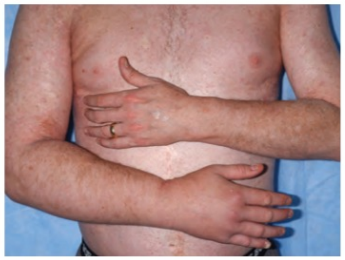
Interventions for improvement of QOL

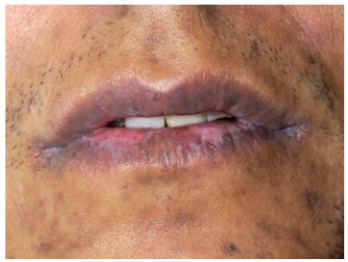
Conclusions

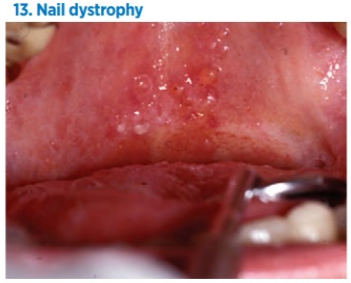
Delayed complications (3°mos -2°ys)
Chronic GVHD

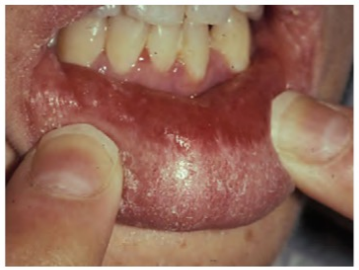

13. Nail dystrophy

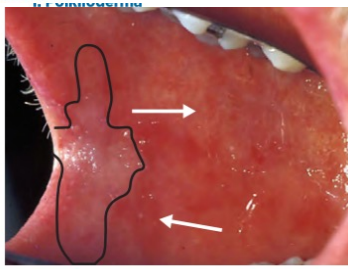

14. Alopecia

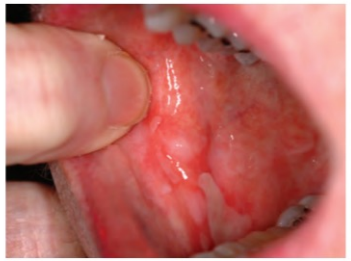

15. Edema

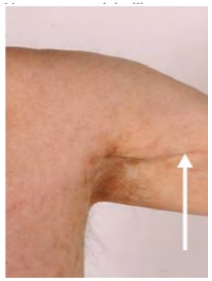

16. Lichen planus

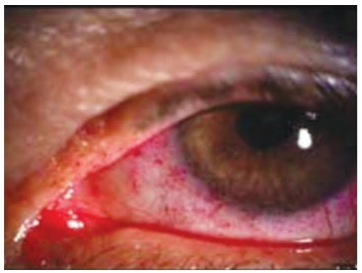

17. Mucoceles

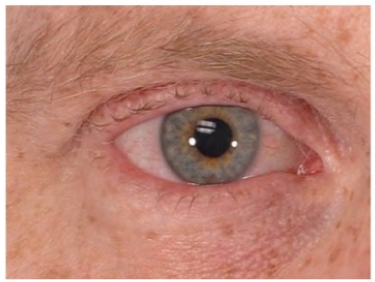

18. Erythema

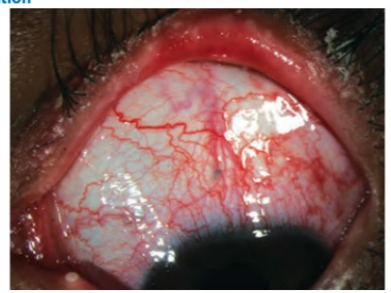

19. Erythema, hyperkeratinization

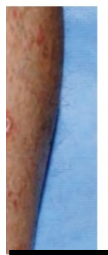

21. Ulcerations


9. Sclerosis, fasciitis


22. Keratoconjunctivitis sicca


23. Keratoconjunctivitis sicca


24. Blepharitis



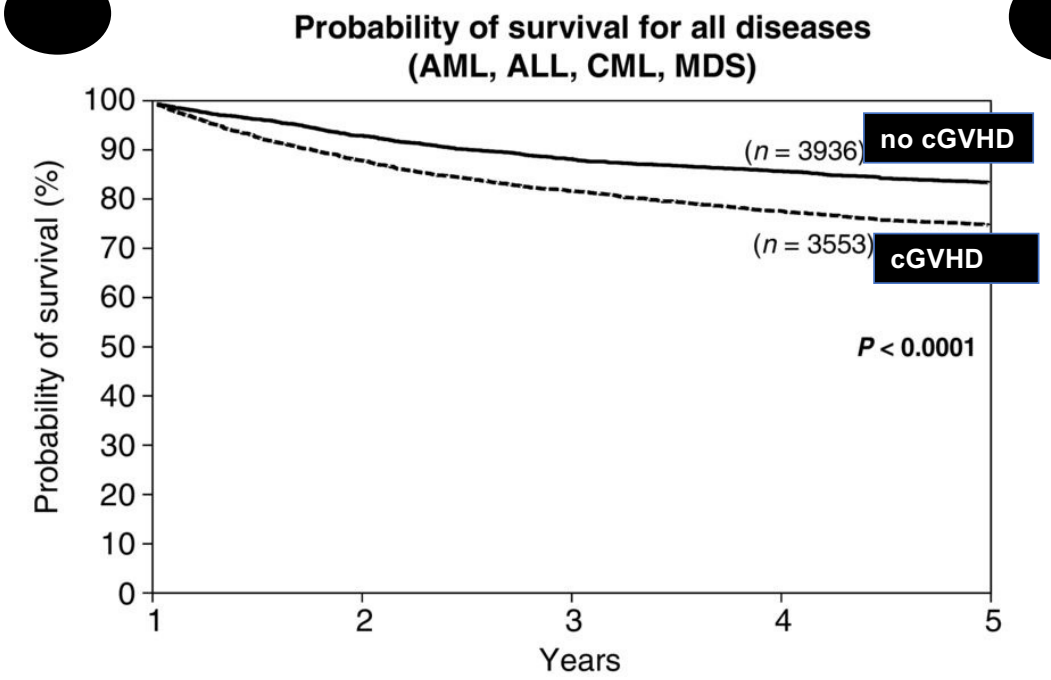
agressive local treatment

most cases resolve within 5 years

minimum systemic therapy

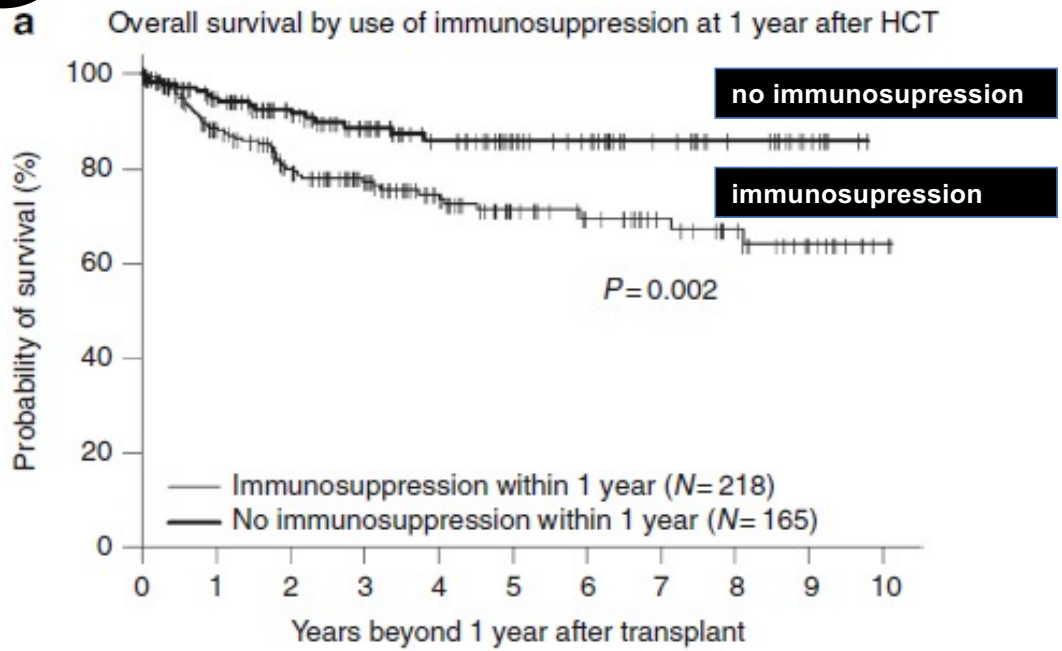
NIH Consensus Jagasia et al. BBMT 2015

Delayed complications
Chronic GVHD and Overall Survival



- 1-year survivors with cGVHD
- Proir history of cGVHD in Pz alive at 1y increases the risk of TRM and decreases OS

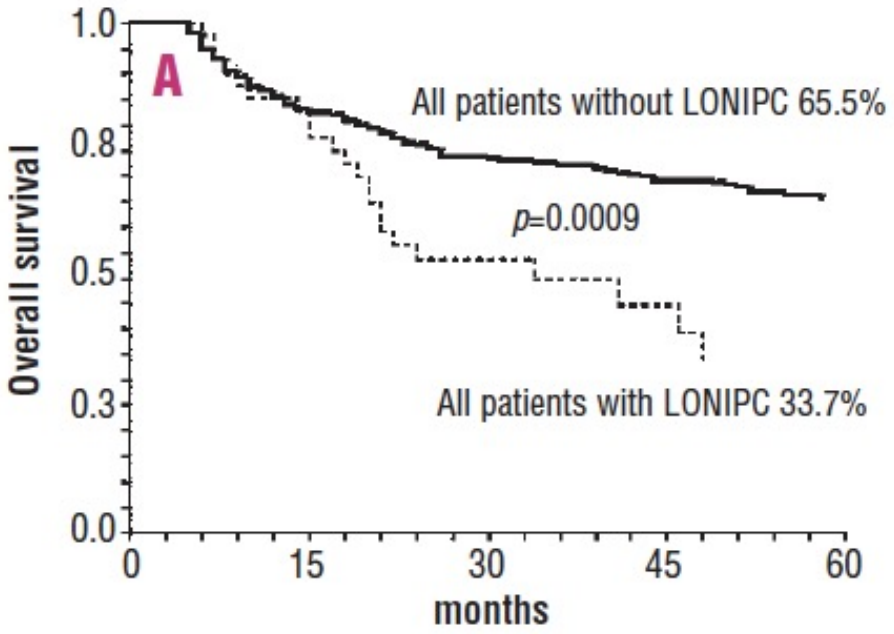
Boyiadzis et al. Clin Cancer Res. 2015

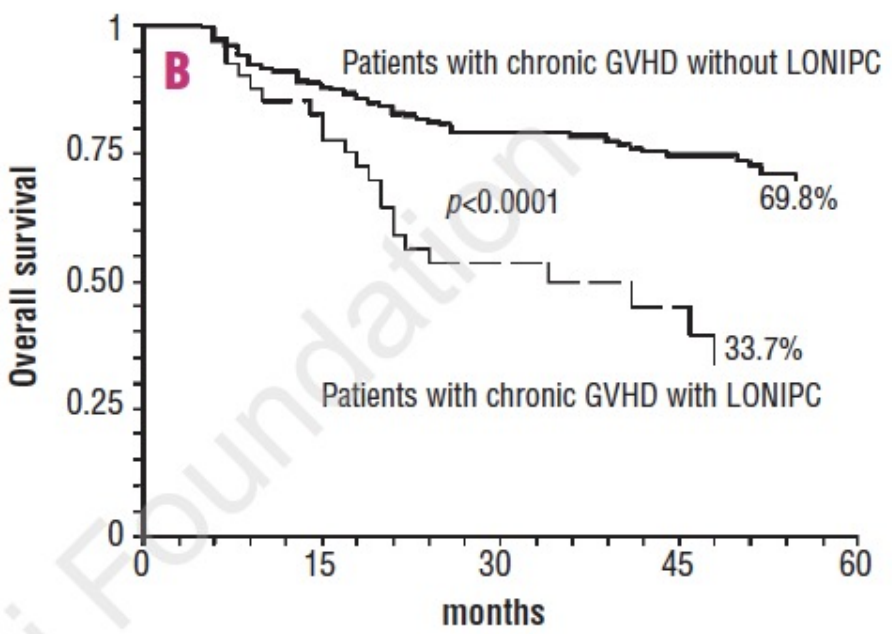


- Most patients die from infectious complications
- immunosupression increases relapse

Solh et al. Bone Marrow Transplant. 2018

Late Onset Non Infective Pulmonary Complications (LONIPCs)



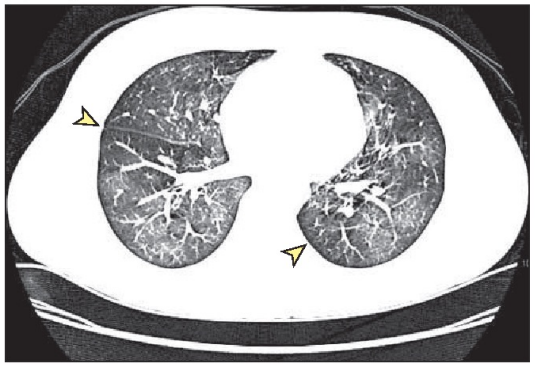


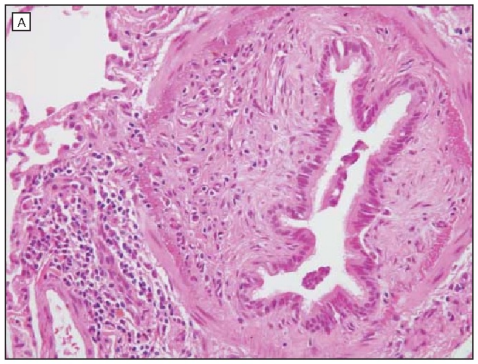
599 allo-SCT performed between 1992 and 2004, in Udine and Bologna
42 LONIPC over 438 patients (10%) surviving more than 3 months after allo-SCT

Figure 1. Comparison of 5-year overall survival between patients with and without LONIPC among (A) all transplanted patients and among (B) patients with chronic GVHD.

Patriarca F et al, Haematologica. 2006

Pulmonary diseases – Bronchiolitis obliterans syndrome (BOS)





Evaluate PFTs:
- FEV1< 75%
- FEV1/**VC** < 90% CI
- Absent infection
- cGVHD *or*
  or air trapping RV >120% or RV/TLC >90% CI
  or air trapping by expiratory CT

Rule out:
- Tracheomegaly
- Alpha-1 antitrypsin
- Cryptogenic organizing pneumonia

Work-up
- Inspiratory/ expiratory CT
- Consider bronchoalveolar lavage
- Blood cx, CMV PCR

Treatment
- FAM +Steroid pulse/rapid taper

Progression:
- ECP
- Etanercept
- Clinical Trials

Supportive care
- PCP ppx
- Fungal ppx (vori or posa if systemic steroid)
- Penicillin ppx
- Pulmonary rehabilitation
- Consider IVIG
- Nutritional support
- GERD therapy

✓ *for Methemoglobinemia if hypoxic*

Bronchiolitis obliterans syndrome (BOS)

- Chronic GVHD expression
- Median 1,5 years
- **Incidence: 5-10%**
- **Prevalence: 15%**
- Silent onset, generally irreversible once symptom appear (dyspnea on exertion, cough, wheezing).

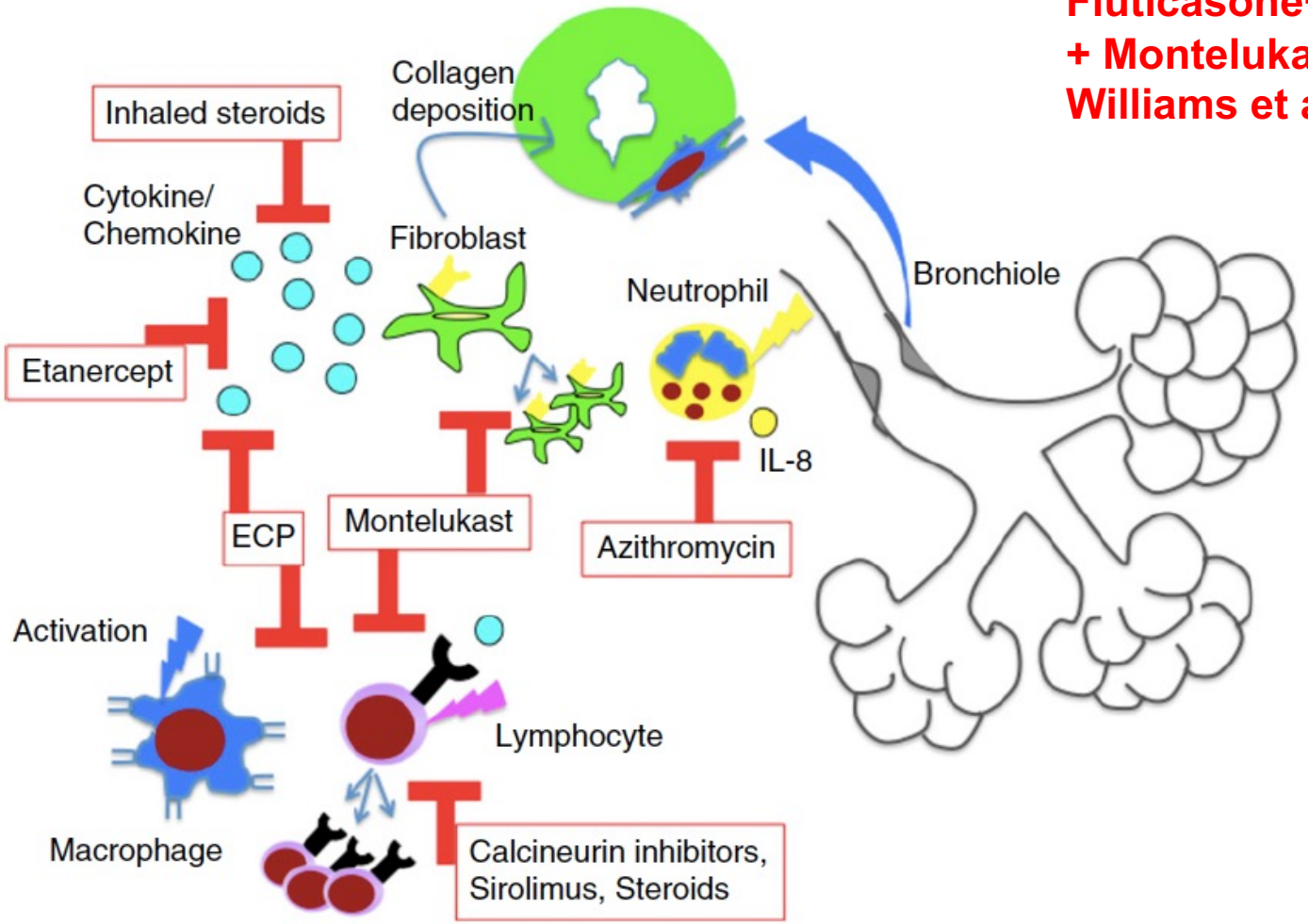
Screening and Treatment

- Pulmonary test including %FEV1 and FEV1/FVC every three months in patient wiht cGVHD,
- Patient with no cGVHD: Pulmonary test every 6-12 months for first 5 years.
- Treatment: prednisone 1 mg/kg
- FAM (inhaleted fluticasone propionate, azithromycin, montelukast)

Williams KM et al, JAMA. 2009; Inamoto Y et al, Haematologica, 2017; Williams KM, Blood. 2017

Bronchiolitis obliterans syndrome (BOS) - Treatment

Fluticasone+Azithromycin + Montelukast
Williams et al. BBMT 2016



William KM, Blood. 2017

Bronchiolitis obliterans syndrome (BOS) – New Perspective

TGF-beta inhibitor

ARTICLE

Check for updates

The safety and tolerability of pirfenidone for bronchiolitis obliterans syndrome after hematopoietic cell transplant (STOP-BOS) trial

JAK 1/2 inhibitor
REACH3 Trial

Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease

TKI inhibitor → **Nintedanib** → **Clinical Trial**

Matthiaou EI et al, BMT. 2022; Zeiser R et al, NEJM. 2021

Delayed complications Lungs

In addition to BOS, other LONIPCs have been described, including

Diffuse interstitial lung disease (ILD), 3-year CI 5% at a median of 100 days

- ILD has been described more recently than BOS and it was associated with restrictive lung disease (RLD).ILDs may correspond to several histological patterns (organizing pneumonia,….)
- In almost all cases, interstitial pathology coexisted with histological lesions of obliterative bronchiolitis.
- The frequent histologic association with obliterative bronchiolitis and clinical association with other manifestations of GVHD raise the question of whether **ILDs could be part of a spectrum of lung cGVHD.**

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Introduction

Delayed complications

Late complications (2-10ys)

Very late complications

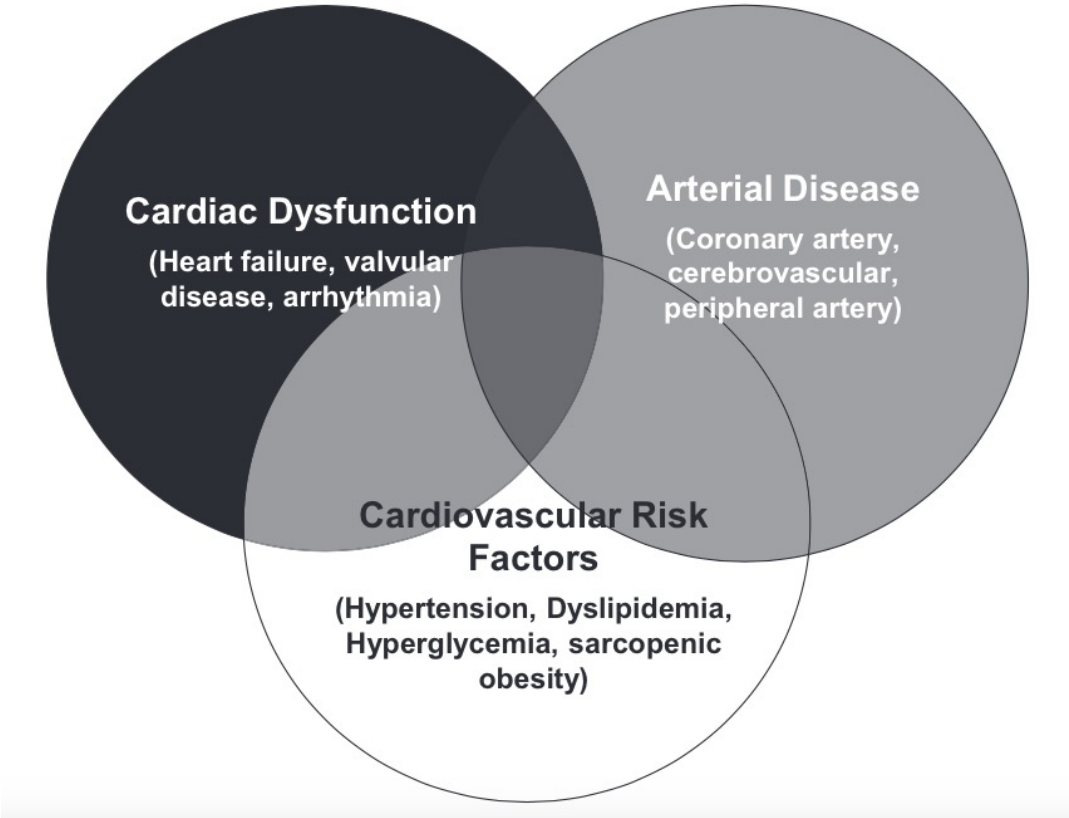
Screening for complications

Symptoms & syndromes/quality of life

Interventions for improvement of QOL

Conclusions

Late complications - Cardiovascular diseases (CVD)



Cardiovascular diseases (CVD)
• **3-4 x higher risk than general population** • **Median age at first Cardiovascular event (myocardial infarction): 53 years** (general population: 67 years) • **Risk: Anthracycline exposure, chest radiation** • Cardiomiopathy, congestive heart failure, valvular dysfunction, arrhythmia, pericarditis and coronary artery disease • **10-years cumulative incidence: 5-10%** • **2-11% mortality among long term survivors**

Screening and Treatment
• Lifestyle modification • Control Blood Pressure (ACE-inhibitors, beta-blockers) • Test: Echocardiogram, BNP, lipid panel, glucose level, Hb1Ac

Armenian SH et al, BBMT. 2017; Inamoto Y et al, Haematologica, 2017

Late complications/Endocrine diseases – Hypotiroidism, Diabetes, Dyslipidemia

Hypotiroidism

- **30% patients by 25 years after HSCT**
- Risk factors: age < 10 years, radiation, conditioning regimen with busulfan or cyclophosphamide.
- Check TSH, fT3, fT4 every year
- Hypertiroidism is very rare.

Diabetes

- **8-41% after alloHSCT, 3% after autoHSCT**
- 3-fold risk respect sibilings

Treatment:

- Life-style modification
- Hypoglicemic agents
- Insulin

Dyslipidemia

- **8-61% HSCT survivors**
- LDL > 130-190 mg/dl start Lifestyle counseling + statin therapy
- TG > 200 mg/dl consider omega-3-acid ethyl esters or fibrate

Late effect	Tests	Preventive approaches	Treatment
Endocrine			
Hypothyroidism	Thyroid-stimulating hormone, thyroxine levels		Replacement therapy
Diabetes	Glucose level, HbA1c, glycoalbumin		Lifestyle modification, hyperglycemic agents, insulin
Dyslipidemia	Lipid panel		Lifestyle modification, statins, fibrates, fish oil (omega-3 fatty acids), ezetimibe
Adrenal insufficiency	Cortisol-stimulation test	Alternate-day regimen when corticosteroids are used	Hydrocortisone, low-dose prednisone

Inamoto Y et al, Haematologica, 2017

Male gonadal dysfunction and infertility

Genital Chronic GVHD

- Incidence: 5-20%
- Time of presentation: 2-6 years after HSCT
- Symptoms: painful intercourse, burning sensation
- Balanoposthitis, lichen sclerosis-like or lichen planus-like features, phimosis, urethral or meatal scarring or stenosis.
- Genitourinary and sexual dysfunction

Sexual dysfunction

- Common: 28-80%
- Correlation with erectile disfuction, loss of sexual interest, ↓libido, ↓enjoyment of sex

Infertility

- Less frequent than women
- Risk factors: Conditioning regimen (TBI)

Hypogonadism

- **Wide range of prevalence: 7-84%**
- Leydig cell are less vulnerable to chemoterapy and radiation respect to germinal epithelium -> Azoospermia and Infertility, but normal testosterone levels
- Compensated Hypogonadism: ↑LH, = Testosterone
- Hypogonadism: ↑LH, ↓ Testosterone
- **Specific Symptoms: loss of body hair, small testes and erectile dysfunction.**
- **Non specific symptoms: loss of libido, anemia, fatigue, lack of motivation, ↓muscle mass, ↑fat mass.**
- Immunosoppressive treatments (Cya, steroids) ↓hypotalamic-pituitary-gonadal axis
- **Treatment: Testosterone replacement**
- **Risk of treatment: polycythemia.**
- **Not given in patients with prostate cancer**

Phelan R et al, BMT, 2022; Inamoto Y et al, Haematologica, 2017

Female gonadal dysfunction and infertility(1)

- **Ovarian insufficiency, vaginal changes and low libido occur in female patients**. Ovarian failure occurred in more than 90% of female patients after HCT and recovered in the majority of them
- The use of **hormone replacement therapy** for premature ovarian failure should be **individualized**
- Efficacy of **gonadotropin-releasing hormone agonists** in preserving fertility in cancer patients is **controversial**
- 0.87% of patients or their partners had **pregnancies after allogeneic** HCT, wait 2-5 years after HCT before attempting conception since rates of relapse are generally highest in the first two years
- **Pregnancy outcomes are generally good** with no increase in the risk of fetal malformations

Female gonadal dysfunction and infertility(2)

63 Pts, allo transplant before 35 ys, follow up > 2 ys,median age at transplant 24,entry study 31, 86% hypoestrogenism,76% sexual disfuntion

Sexuality- and Fertility-Related Issues in Women after Allogeneic Hematopoietic Stem Cell Transplantation

Nathalie Forgeard[1], Matthieu Jestin[1], Dominique Vexiau[2,3], Florian Chevillon[1,4], Elise Ricadat[5], Régis Peffault de Latour[6,7], Marie Robin[7], Flore Sicre de Fontbrune[7], Aliénor Xhaard[7], David Michonneau[6,7], Nicolas Boissel[1,4], Catherine Poirot[1,8], Nathalie Dhédin[1,*]

[1] *Service d'Hématologie Adolescents Jeunes Adultes, Hôpital Saint-Louis, AP-HP, Paris, France*
[2] *Service de Dermatologie, Hôpital Saint-Louis, AP-HP, Paris, France*
[3] *Centre universitaire du diabète et de ses complications, Hôpital Lariboisière, AP-HP, Paris, France*
[4] *EA-3518, Institut de Recherche Saint-Louis, Université de Paris, Paris, France*
[5] *Université de Paris, IHSS/CRPMS/IUH, 75013, Paris, France (Research conducted under the Institut La Personne en Médecine, ANR-18-IDEX-0001)*
[6] *U976, Institut de Recherche Saint-Louis, Université de Paris, Paris, France*
[7] *Service d'hématologie-greffe, Hôpital Saint-Louis, AP-HP, Paris, France*
[8] *Médecine Sorbonne Université, 75005 Paris, France*

13 PREGNANCIES,8 SPONTANEOUS,5 ART,POST RIC

Forgeard N et al, Transplantation and Cellular Therapy, 2020

EBMT

136 allo patients
81 partners

www.nature.com/bmt

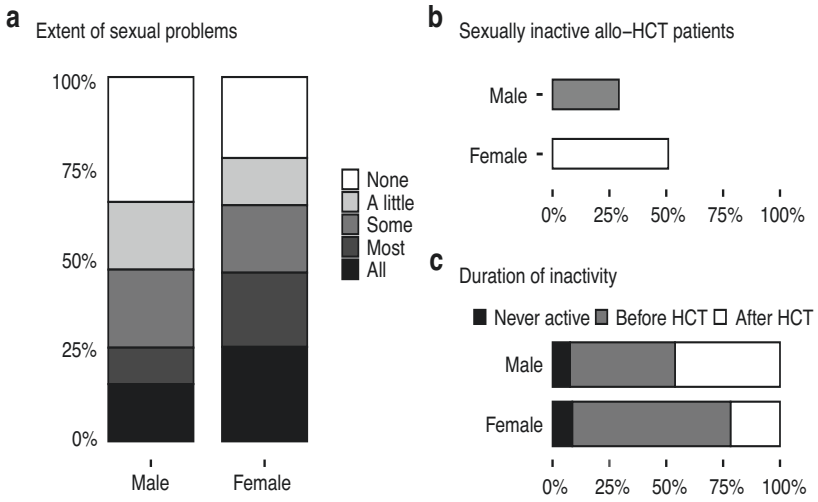
ARTICLE

Check for updates

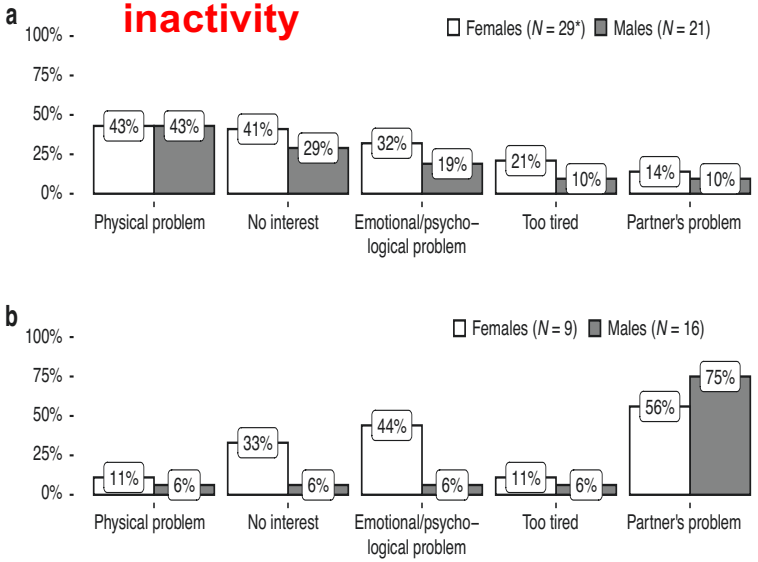
Sexual function of adult long-term survivors and their partners after allogeneic hematopoietic cell transplantation in Europe (S-FAST): a study from the Transplant Complications Working Party and Nurses Group of the EBMT

Lars Klingen Gjærde[1,2,23], Corien Eeltink[3,23], Jacqui Stringer[4,5], Jarl Mooyaart[6], Paul Bosman[7], Michelle Kenyon[8], Sarah Liptrott[9], Diana M. Greenfield[10], Andrea Linke[11], Pascal Turlure[12], Stefano Botti[13], Dzenana Dzaferagic[14], Simona Sica[15,16], Lorna Welsh[17], Annika Kisch[18,19], Zinaida Perić[20], Hélène Schoemans[21,22,23] and John Murray[4,23]✉

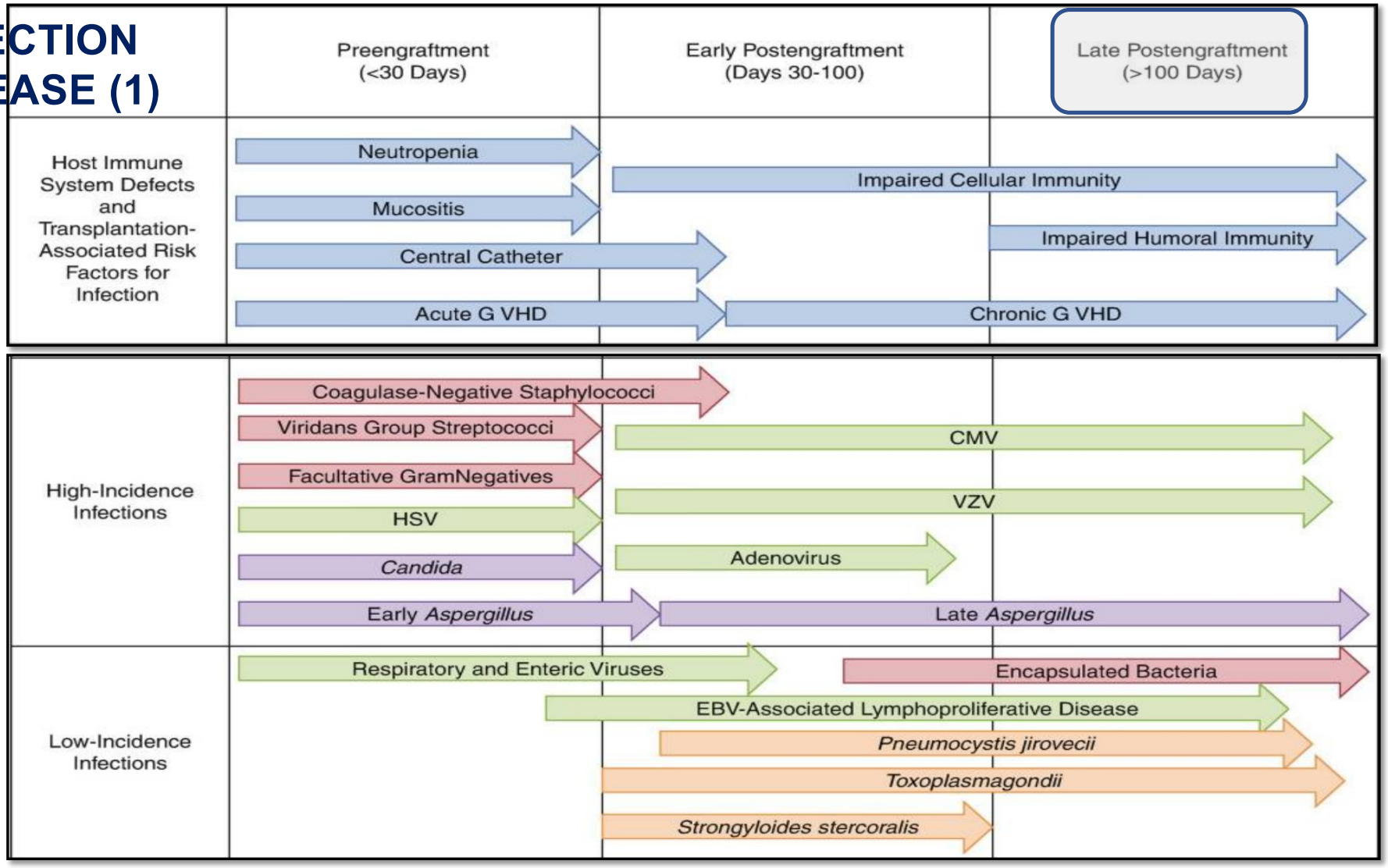
Sexual problems and inactivity



Reasons for sexual inactivity



INFECTION DISEASE (1)



Pereira et al, 2018

Infectious disease(2) – Late fatal infection-LFI

CIBMTR,retrospective study,1995-2011,allo,15.000 Pts surviving 2 ys, 2245+377 deaths, LFI 30%

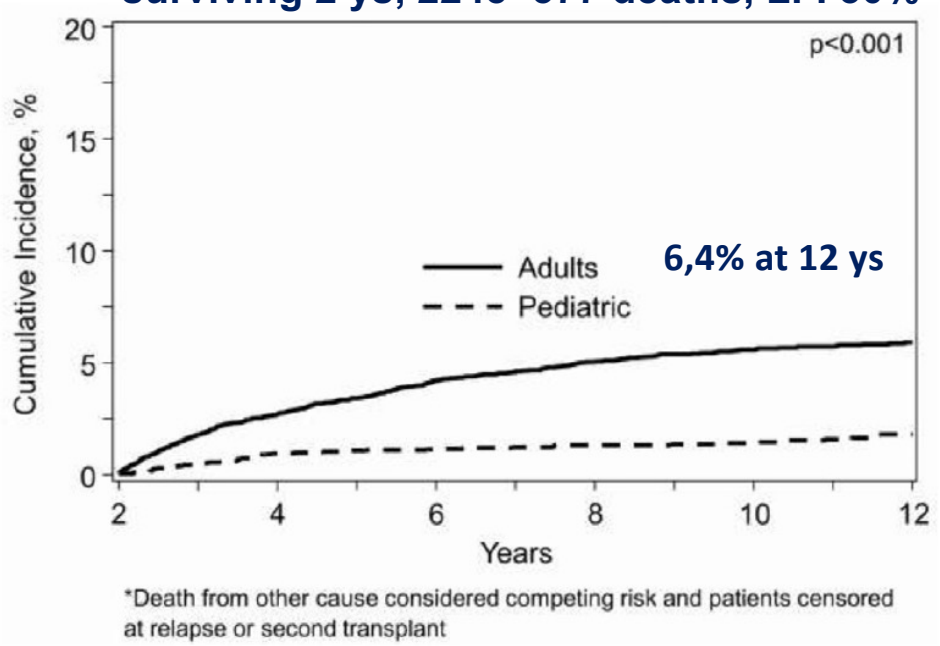


Figure 1. Cumulative incidence of death from infection after 2 years of survival in adult and pediatric patients. *Death from another cause was considered a competing risk, and patients were censored at relapse or second transplantation.

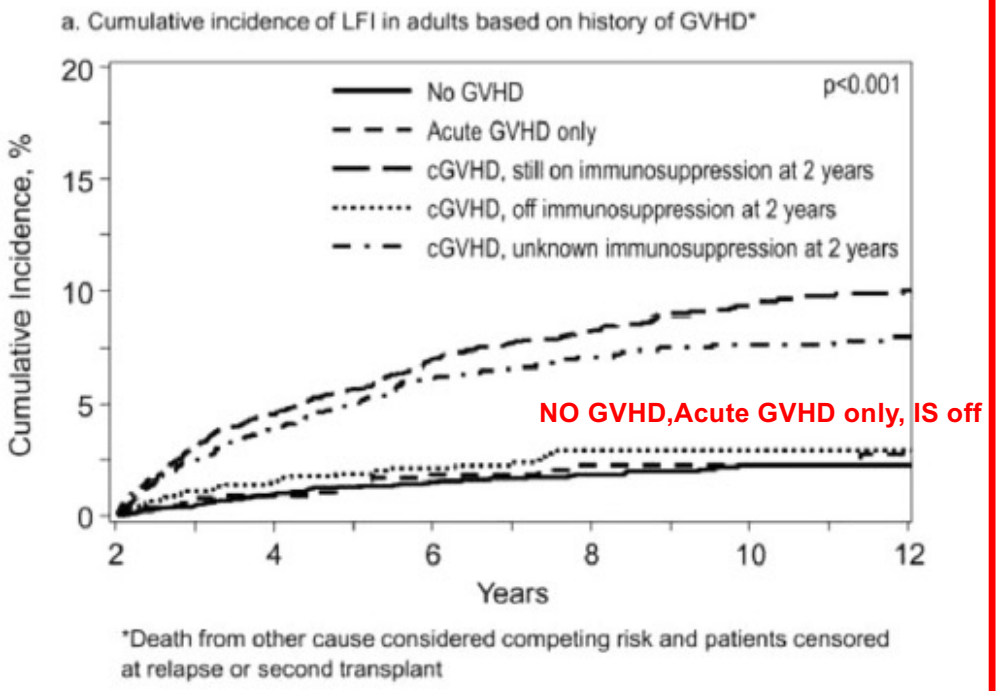
Table 2
Types of LFI in HCT Recipients Who Were Disease-Free for at Least 24 Months after Transplantation

Parameter	Value	
	Adult	Pediatric
LFI Patients who died from infection, n*	496	68
Infection listed as the primary cause of death, n (%)	311	41
Bacterial	108 (35)	13 (32)
Viral	29 (9)	0
Fungal	35 (11)	7 (17)
Protozoal	1 (<1)	0
Unspecified	116 (37)	20 (49)
Multiple types reported	22 (7)	1 (2)
Infection listed as contributing cause of death, n (%)	185	27
Bacterial	85 (46)	10 (37)
Viral	29 (16)	5 (18)
Fungal	20 (11)	4 (15)
Protozoal	0	0
Unspecified	49 (26)	8 (30)
Multiple types reported	2 (1)	0

* Patients with relapse or second HCT occurring ≥2 years after HCT were censored at the event and excluded from this analysis.

Norkin M et al, BBMT. 2019

Infectious disease(3) – Late fatal infection



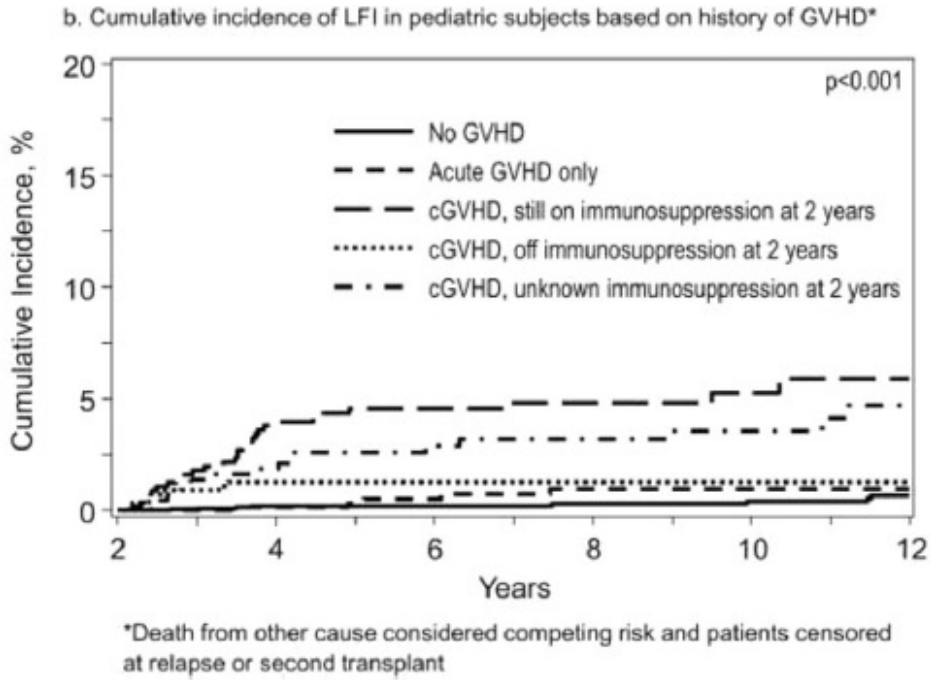


Figure 2. (A) Cumulative incidence of LFI in adults based on history of GVHD. (B) Cumulative incidence of LFI in pediatric patients based on history of GVHD.

Norkin M et al, BBMT. 2019

EBMT European Society for Blood and Marrow Transplantation

Introduction

Delayed complications

Late complications

Very late complications (>10ys)

Screening for complications

Symptoms & syndromes/quality of life

Interventions for improvement of QOL

Conclusions

Very late complications
Cardiovascular events

- CI of cardiovascular event raises to 22% at 25 years
- cardiovascular death 2x more frequent
- endothelial injury (TBI) – accelerated atherosclerosis*
- Metabolic syndrome:

Hypertension	**Dyslipidemia**
Obesity	**Diabetes**

49% after allo-SCT versus 30% in general population**
the precise relationship between HCT, MetS and CV disease needs further clarification

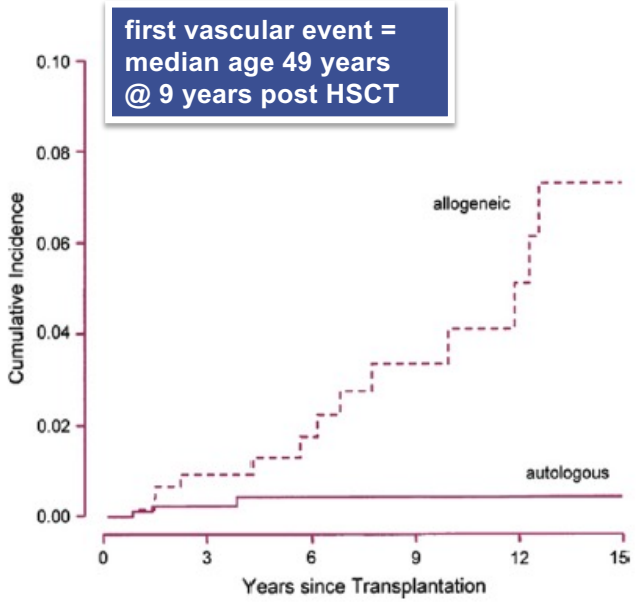


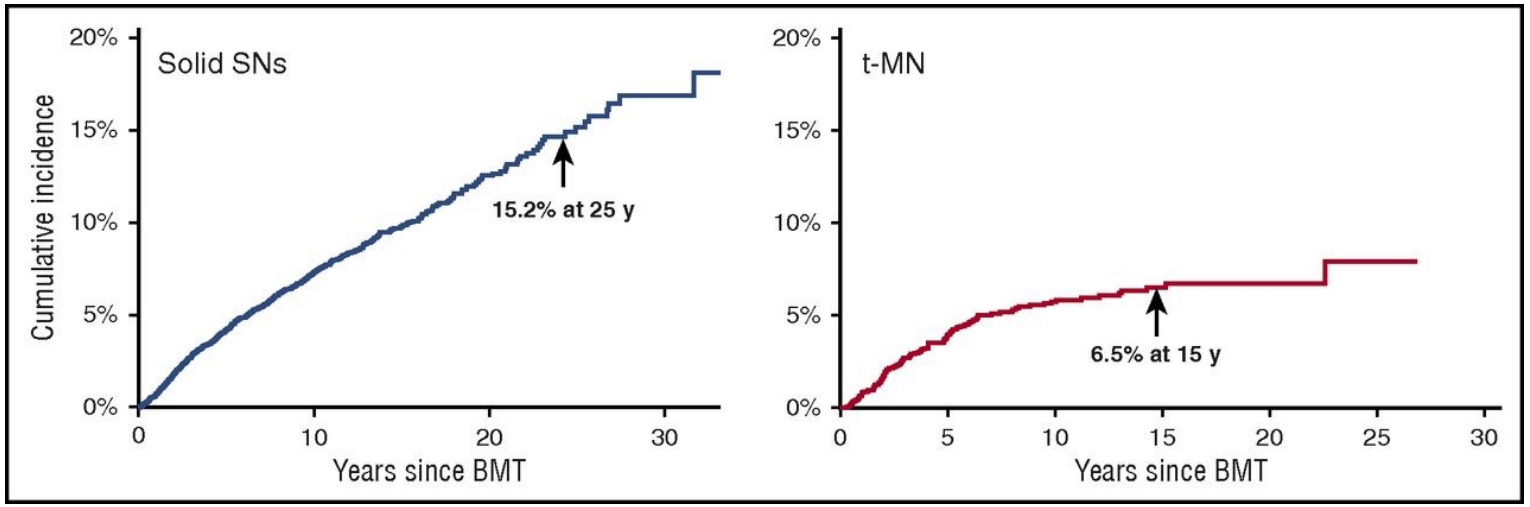
Figure 1. The cumulative incidence of cardiovascular event at 15 years, adjusted for age. Using an adjusted Cox model, the relative risk is significantly higher after allogeneic than after autologous HSCT. This research was originally published in *Blood*. Tichelli A, Bucher C, Rovo A, et al. Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. 2007;110:3463–71. © the American Society of Hematology.[3]

*Armenian et al, BBMT 2017, **Majhail et al BMT 2009

Very late complications
Subsequent neoplasms

- 2-3x more frequent then in ’normal population’*

- early (in first 6 months)- PTLD (post-transplantation lymphoproliferative disease)
- median 2-3 years – secondary myelodysplasia
- solid tumours after 10 years (radiaton - breast, thyroid, sarcoma, chronic GVHD – skin, mouth)



*Rizzo et al, Blood 2009
Bhatia Thomas’
Hematopoietic Cell Transplantation.
5th ed. 2016

JAMA Oncology | Original Investigation

Evaluation of Second Solid Cancers After Hematopoietic Stem Cell Transplantation in European Patients

André Tichelli, MD; Eric Beohou; Myriam Labopin, MD; Gérard Socié, MD; Alicia Rovó, MD; Manuela Badoglio; Anja van Biezen; Peter Bader, MD; Rafael F. Duarte, MD; Grzegorz Basak, MD; Nina Salooja, MD; for the Transplant Complications Working Party of the EBMT

EBMT retrospective study

All patients who underwent a transplant in Europe and had a second solid cancer diagnosis between January 1,2000 and December 31,2014.

RESULTS In total, 220 617 patients underwent a transplant, of whom only 4065 (1.8%) patients with a second solid cancer after HSCT were included in the study. Among the 4065 patients, 2321 (57.1%) were men and 1744 (42.9%) were women, with a mean (range) age of 59.1 (3.2-82.3) years at diagnosis of second solid cancer. The 5-year age-standardized overall survival was 47% (95% CI, 45%-49%). The 5-year overall survival rate after SSC diagnosis was poor for pancreas, lung, hepatobiliary, esophageal, brain, and gastric cancers, with a median survival between 0.6 and 1 year. The 5-year overall survival was intermediate for endometrial, colorectal, sarcomas, ovarian, bladder, oropharyngeal, and kidney cancers, with a median survival between 2 and 10 years. The 5-year overall survival was more favorable for melanoma, breast, prostate, cervix, and thyroid cancers, with a median survival of 10 or more years. Additional transplant-associated factors for mortality for patients treated with allogeneic HSCT were age at transplant, donor type, conditioning regimen, and graft-vs-host disease. In total, 1777 patients (43.7%) died, of which 1256 (74.8%) were from SSC, 344 (20.5%) from primary disease, and 79 (4.7%) from other causes. Standardized mortality ratio was higher, compared with de novo solid cancers, for melanoma, prostate, breast, kidney, bladder, colorectal, and endometrial cancers but not for the other cancers.

Ticheli A et al, JAMA Oncology. 2018

Table. Median Survival, Age-Standardized Overall Survival, and Cumulative Incidence of Death From Second Cancer

Outcome	Second Solid Cancer	HSCT						
		All (N=4065)			Allogeneic (n=1443)		Autologous (n=2622)	
		No. of Patients	5-y OS (95% CI), %[a]	5-y Cumulative Incidence (95% CI), %[b]	No. of Patients	5-y OS (95% CI), %[a]	No. of Patients	5-y OS (95% CI), %[a]
Favorable	Thyroid	149	83 (76-92)	9 (4-7)	78	90 (81-99)	71	77 (65-91)
	Cervix	57	70 (57-86)	15 (6-26)	35	73 (57-93)	22	70 (53-94)
	Prostate	410	69 (64-75)	14 (10-18)	93	72 (61-85)	317	68 (62-75)
	Breast	547	69 (64-74)	13 (10-17)	196	70 (62-78)	351	69 (63-76)
	Melanoma	343	68 (62-74)	22 (17-27)	160	76 (68-84)	183	61 (53-70)
Intermediate	Kidney	177	55 (47-65)	24 (17-32)	47	71 (58-86)	130	51 (42-63)
	Oropharyngeal	207	53 (46-62)	31 (24-39)	104	53 (42-65)	103	55 (44-67)
	Bladder	144	49 (39-62)	25 (17-35)	31	41 (23-74)	113	51 (40-65)
	Ovarian	77	43 (32-58)	42 (29-54)	26	50 (34-75)	51	39 (26-59)
	Sarcomas	215	42 (34-51)	47 (39-55)	96	56 (46-69)	119	31 (23-44)
	Colorectal	446	41 (36-48)	39 (33-44)	121	48 (38-60)	325	39 (33-47)
	Endometrial	46	40 (26-63)	45 (27-61)	26	58 (39-86)	20	18 (5-60)
Poor	Gastric	158	29 (21-39)	58 (48-66)	57	37 (26-54)	101	22 (13-37)
	Brain	156	21 (15-30)	63 (53-71)	71	20 (12-36)	85	22 (14-35)
	Esophageal	88	21 (13-36)	61 (48-72)	53	23 (12-43)	35	20 (9-45)
	Hepatobiliary	90	18 (11-31)	74 (61-84)	32	15 (5-40)	58	21 (12-37)
	Lung	597	14 (11-19)	74 (69-78)	179	16 (11-24)	418	14 (10-19)
	Pancreas	145	8 (3-18)	89 (79-94)	36	15 (6-36)	109	6 (2-19)

Abbreviations: HSCT, hematopoietic stem cell transplantation; OS, overall survival.

[a] 5-y age-standardized OS.

[b] 5-y cumulative incidence of death from second cancer (competing risk: death from any other cause).

Ticheli A et al, JAMA Oncology. 2018

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Introduction

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Very late complications

Screening for complications

Symptoms & syndromes/quality of life

Interventions for improvement of QOL

Conclusions

Complications
Screening, Prevention

TIMING	FOLLOW-UP	SCREENING	PREVENTION
first 100 days	1x weekly 1x two weeks 1x monthly	acute GVHD infections	acute GVHD infections
after 6 months	1x 2-3 months	chronic GVHD (eyes, mouth, skin) + pulmonary function -> stop immunosupression	immune status; stop antibiotics> vaccination
after 1 year	1x 6 months	chronic GVHD+pulmonary function, endocrine assesment (gonads, thyroid); DXA scan	cardiovascular risks (DM; AH, lipidemia) secondary cancers
after 2 years	1x year	all organs	cardiovascular risks secondary cancers

**Majhail et al. BMT 2012*

Recommended practice

Delayed complications

- Evaluate GvHD regularly up to two years post HSCT
- Evaluate Pulmonary Function Tests
- Prophylaxis for encapsulated bacteria, aspergilosis, VZV, PCP
- Start vaccinations with inactivated vaccines from 3 months

ECIL 7, Cordonnier et al. Lancet Infect Dis 2019

Late complications

Screen for

thyroid dysfunction, hypogonadism, renal impairment

Evaluate DXA scan and heart function

Majhail et al. BMT 2012

Very late complications

Screen for cardiovascular risks at 1 year and then yearly, treat MS

Educate on "healthy life style" - obesity

Screen for malignancies yearly (skin, mouth, self-examination)

Encourage to reduce UV skin exposure

In women after TBI/chest radiation perform mammography

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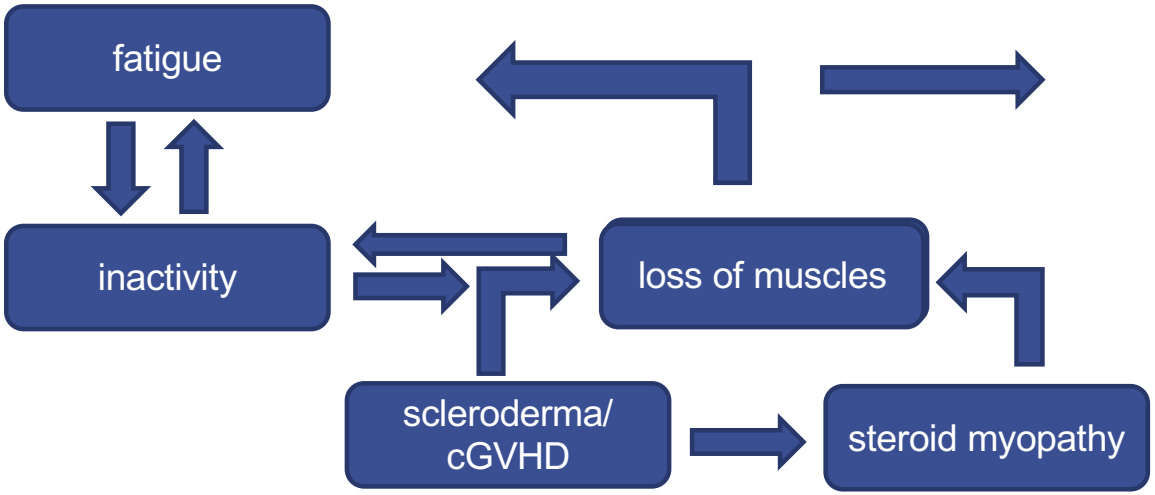
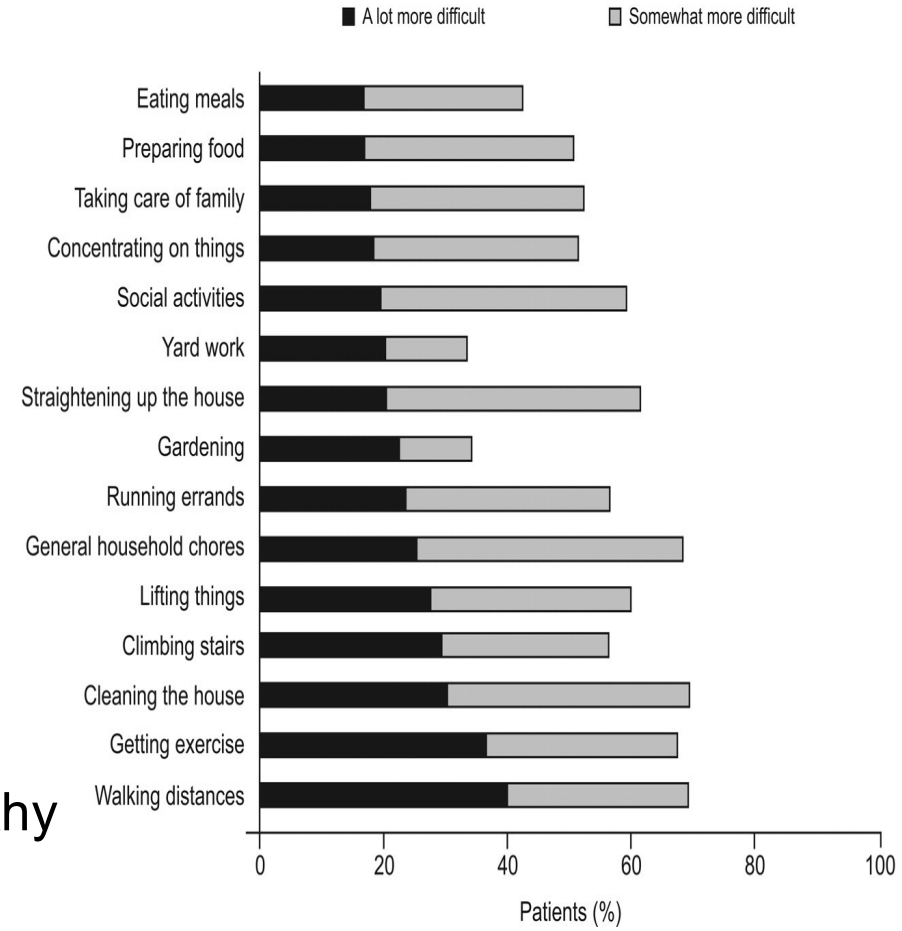
Symptomes and Syndromes
Fatigue

- in first 2 years 40% patients have fatigue*
- at 10 years symptoms still in 35% patients



- DD:GVHD polimyositis/steroid miopathy/neuropathy
- Th: physical exercise/psychostimulants

*Bevans et al BBMT 2017



Hofman et al. The Oncologist 2007

Symptomes and Syndromes
Emotional distress

- emotional recovery lasts more than 2 years
- cumulative incidence of depression 9-20%

• fear from relapse	post-trauma grow
• anxiety about check-ups	gratitude
• stress due to incertainity	
• GVHD symptoms	

- psychological assessment yearly*

Did you feel sad, depressed or hopeless in last 2 weeks?

Did you feel down and not interested for every day duties?

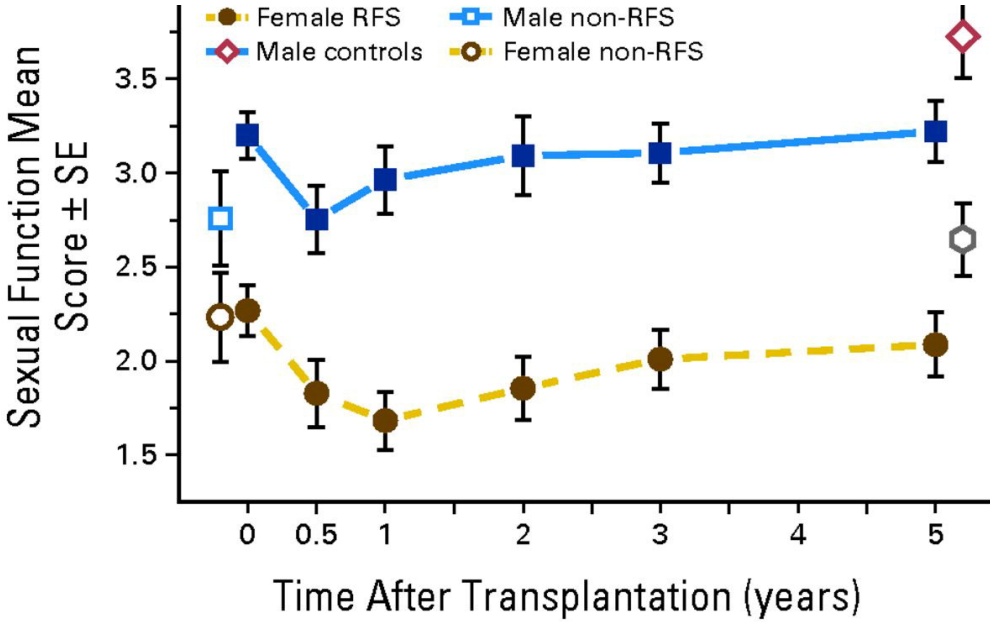
***Majhail et al. BMT 2012**

Symptomes and Syndromes
Sexual problems

hormonal disbalance

chronic GVHD

psychological adjustment



- most males return to normal after 1-2 years
- 45% women never return to normal
- Th: hormonal + local th (GVHD) + counselling

Syrjala Blood 2008

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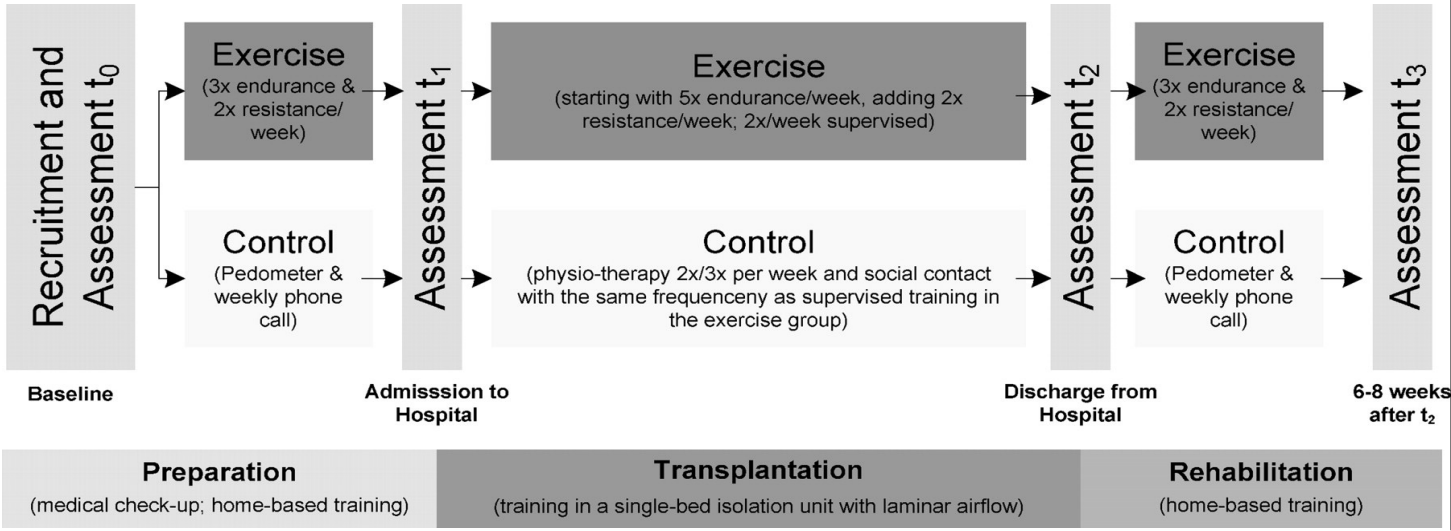
Randomized studies* exercise
improve fatigue, physical recovery, QOL and long-term outcomes
Carlson BMT 2006; Lemercier Ann Phys Rehabil Med 2014; Wilson BMT 2005; Wiskemann Blood 2011



Quality of life Interventions

exercise
survivorship care plan
cGVHD team

Clin Transplant 2013: 27: E1–E2 DOI: 10.1111/ctr.12051

Clinical Transplantation

Letter to the Editor

A dedicated GvHD clinic may improve the quality of life for allogeneic stem cell transplant survivors

Ferrata Storti Foundation

Randomized controlled trial of individualized treatment summary and survivorship care plans for hematopoietic cell transplantation survivors

Navneet S. Majhail,[1] Elizabeth Murphy,[2] Purushottam Laud,[3] Jaime M. Preussler,[2,4] Ellen M. Denzen,[2,4] Beatrice Abetti,[5] Alexia Adams,[4] RaeAnne Besser,[4] Linda J. Burns,[2,4] Jan Cerny,[6] Rebecca Drexler,[4] Theresa Hahn,[7] Lensa Idossa,[2] Balkrishna Jahagirdar,[8] Naynesh Kamani,[9] Alison Loren,[10] Deborah Mattila,[4] Joseph McGuirk,[11] Heather Moore,[2] Jana Reynolds,[12] Wael Saber,[3,13] Lizette Salazar,[14] Barry Schatz,[15] Patrick Stiff,[15] John R. Wingard,[16] Karen L Syrjala[17] and K. Scott Baker[17]

Haematologica 2019
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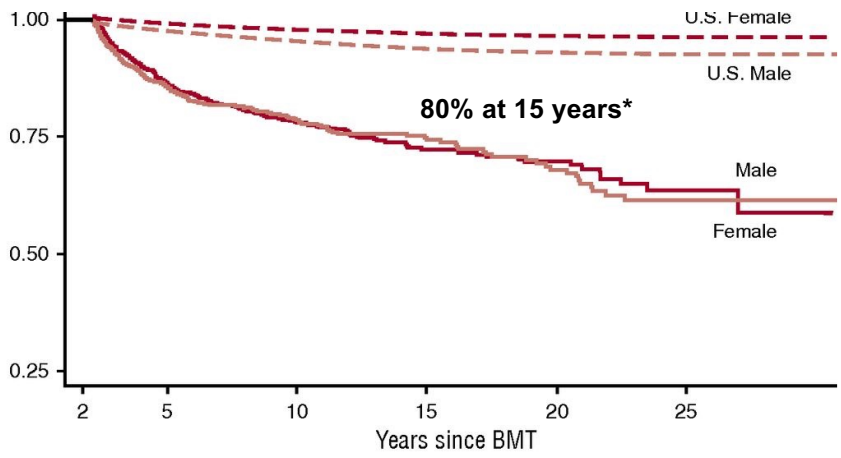
PREMATURE AGING



Causes of late death: relapse (14%)**
infections (12%)
GVHD (11%)
cardiovascular disease (12%)
subsequent neoplasms (11%)

- 2/3 patients have at least one late complication
- 15-year CI of serious late complications is 40%

- more than 40% patients experience fatigue, sexual and cognitive impairment
- up to 30% suffer from anxiety and depression

- 30-40% do not return to work = reintegration

- NIH Blood and Marrow Transplant Late Effects Consensus Conference 2016***: recognize, treat, prevent

Bhatia et al Blood 2007, **Marin et al, JCO 2010*

****Battiwalla et al, BBMT 2017*

Conclusions – Can we do better?

- Road map for survivorship
- Clinical model for continue follow up
- Multisciplinary approch

Periodical cancer screening