Busulfan/Cyclophosphamide (BuCy) versus Busulfan/Fludarabine (BuFlu) Conditioning Regimen Debate

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Disclosures

- Donald Hutcherson
  - Nothing to disclose
- Ashley Engemann
  - Astellas Advisory Board Participant
- Off-label use of medications will be discussed

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Learning Objectives

- Compare the efficacy of the busulfan/cyclophosphamide (BuCy) and busulfan/fludarabine (BuFlu) conditioning regimens in allogeneic hematopoietic cell transplant (HCT) recipients with myeloid malignancies
- Describe the toxicity profiles of BuCy and BuFlu conditioning in this setting
- Explain the advantages and disadvantages of BuCy and BuFlu conditioning
- Identify appropriate candidates for BuCy and BuFlu conditioning

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ARS Question

BuCy and BuFlu are equally efficacious conditioning regimens in patients with myeloid malignancies

1. True
2. False
3. It depends

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ARS Question

Regimen-related toxicity is lower with which of the following when compared to the other?

1. BuCy
2. BuFlu
3. Toxicity is similar

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Background

Busulfan and Cyclophosphamide (BuCy)

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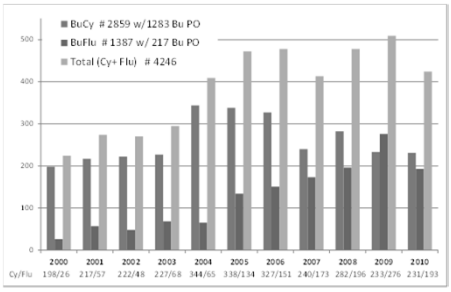
CIBMTR Data 2000 to 2010

Allo Myeloablative Bu with either Cy or Flu



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What do we know about BuCy?

- Bu IV 0.8 mg/kg and Oral 1 mg/kg are not equal.
  - IV 0.8 Bu mean AUC 1106 (413 to 2511) for 1st dose.
  - Oral Bu 1 mg/kg mean AUC 1350-1400
  - Oral exposure has higher interpatient variability plus intrapatient variability and often repeated doses due to vomiting.
  - Different exposure would be expected to give different results and possibly side effect profiles.
  - IV Bu mean T1/2 = 2.83 h (1.69-6.81)

Slattery JT, Letter to Editor. BBMT 2003;9:282-284; Andersson BBMT 2002; 8:145-154.

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What do we know about BuCy?

- Oral standard dosing Bu w/o pk monitoring gives poorer outcomes in 31 Vs. 61 IV BuCy 0.8 mg/kg .
  - Hepatic VOD (HVOD) 10/30 = 30% (6 severe) : 5/61 =8.2% (2 severe)
  - HVOD mortality: 6/30 = 20% : 2/61 = 3%
  - 100 Day mortality: 10/30 = 30% : 8/61 = 13%
  - Other deaths: GVHD 1, Resp failure 1, infection 2 : Resp failure 2, Pneumonia 2, Alveolar hemorrhage 1, disease progression 2

Kashyap, et al. BBMT 2002;8:493-500.

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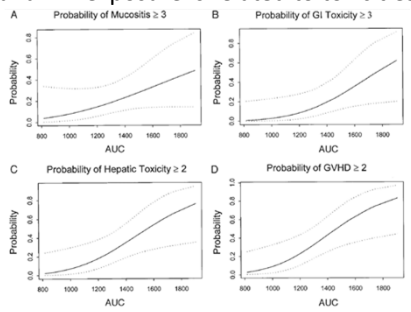
What do we know about BuCy?

- Busulfan IV exposure is related to toxicities



Andersson B, et al. BBMT 2002;8:477-485.

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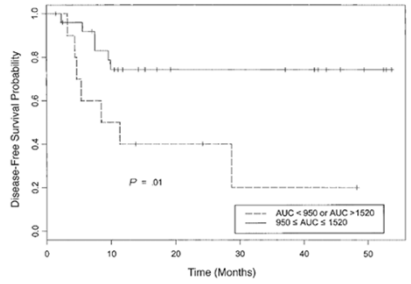
What do we know about BuCy?

- Busulfan IV exposure is related to survival.



Andersson B, et al. BBMT 2002;8:477-485.

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Background

Busulfan and Fludarabine (BuFlu)

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Background: BuFlu

- Busulfan and fludarabine introduced in 2000s as a "myeloablative, reduced-toxicity" conditioning regimen for HCT in patients with myeloid malignancies
- Rationale for once daily dosing of fludarabine followed by busulfan
  - Synergy expected with administration of fludarabine prior to busulfan
    - Fludarabine potentiates alkylator-induced cell killing by inhibiting DNA damage repair
  - Fludarabine has immunosuppressive properties similar to cyclophosphamide
  - Fludarabine has minimal potential to cause veno-occlusive disease
  - Convenient dosing schedule

Russell JA, et al. Biol Blood Marrow Transplant 2002;8:468-76.
Bornhauser M, et al. Blood 2003;102:820-6.
de Lima M, et al. Blood 2004;104:857-64.

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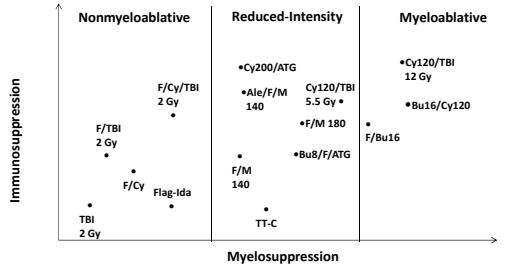
Conditioning Regimen Intensity



Adapted from Baron F and Storb R. Molec Ther 2006;13:26-41.
Ale=alemtuzumab; ATG=antithymocyte globulin; Bu=busulfan; Cy=cyclophosphamide; F=fludarabine; Flag-Ida=fludarabine, cytarabine, filgrastim, idarubicin; M=melphalan; TBI=total body irradiation; TT-C=

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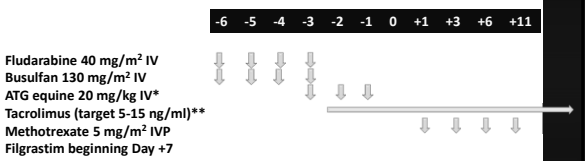
Background – BuFlu Conditioning Regimen



*Tacrolimus continued for 6-8 months
**ATG= antithymocyte globulin; added if one-antigen mismatched related donor or MUD

de Lima M, et al. Blood 2004;104:857-64.

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Background – BuFlu Patient Characteristics

- Patient characteristics
  - 74 patients with AML
    - Failed induction or in 1st CR with high-risk disease or CR2 or beyond
  - 22 patients with MDS
    - High IPSS >=2 or progression after chemotherapy
  - Median age 45 (19-66)
  - 20% in 1st CR; 54 patients with active disease
  - Donor type
    - HLA-compatible related n=60
    - MUD n=36
  - Cell source
    - 49% bone marrow
    - 51% peripheral blood

de Lima M, et al. Blood 2004;104:857-64.

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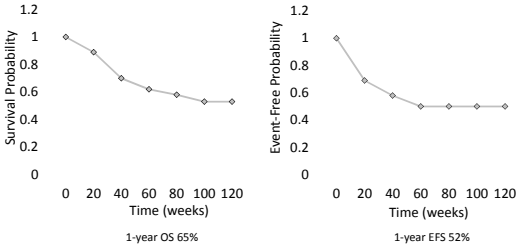
Background – BuFlu Efficacy

Overall Survival and Event-Free Survival



1-year OS 65%

1-year EFS 52%

Adapted from de Lima M, et al. Blood 2004;104:857-64.

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Background –BuFlu Toxicity

- Additional results
  - Median time to neutrophil engraftment 12 days
  - Median time to platelet engraftment 13 days
  - 1-year regimen-related and treatment-related mortality 1% and 3 %, respectively
    - 1 regimen-related death (engraftment syndrome/pulmonary hemorrhage)

de Lima M, et al. Blood 2004;104:857-64.

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Background – BuFlu Toxicity

- Additional results
  - Transient LFT elevation common
  - 2 patients with reversible VOD
  - Grade 3 mucositis, diarrhea, abdominal pain 13%
  - Hemorrhagic cystitis 3%
  - Hand-foot syndrome 4%
  - Graft-versus-host disease
    - — Acute 94% overall
      - Grades II-IV 25%
      - Grades III-IV 5%
    - — Chronic 55% overall

de Lima M, et al. Blood 2004;104:857-64.

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BuFlu Regimen: Busulfan Exposure

- Comparison to IV q6h dosing schedule
- For once daily IV dosing 130 mg/m^2 (3.2 mg/kg), mean daily AUC 4871 uMol x min
- For IV q6h dosing 0.8 mg/kg, mean AUC for dosing interval 1292 uMol x min

Madden T, et al. Biol Blood Marrow Transplant 2007;13:56-64.

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Supporting Argument in Favor of BuCy

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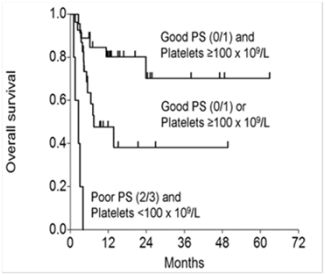
Oral BuCy similar to BuFlu



- Event Free Survival curves were superimposable (~34% at 2 yrs).
- Regimens had identical efficacy in this small analysis.
- Poor PS & low Plts lowered EFS.

Altman J, et al. Blood 2006; 108: Abstract 2940.

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Oral BuCy similar to BuFlu

- Review of 24 Oral Bu PO (14mg/kg) + Cy (120 mg/kg) Vs. 31 IV Bu (520 mg/m^2) + Flu 160 mg/m^2)
- AML, MDS, Lymphoma, CLL, CML/MPD & ALL
- GVHD proph: Csa + Mtx in Cy : Tac + Mtx in Flu
- Cy Vs. Flu: matched related donor 92% : 61%, Refractory disease 50% : 52%, Plts < 100 38% : 45% , ECOG PS 2-3 25% : 13%
- Oral Bu is rarely used for Allo HCT in current practices.

Altman J, et al. et al. Blood 2006; 108: Abstract 2940.

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Cy had better chimerism than Flu

- Retrospective study of 20 BuCy and 20 BuFlu from May 2005 to Jan 2008. Diseases?
- Bu IV 3.2 mg/kg D -7 to -4 & Cy 60 mg/kg D -3 to -2 vs Bu IV 3.2 mg/kg D -5 to -2 & Flu 40mg/m^2 D -5 to -2. (no PK)
- The two groups had similar characteristics.
- Hematopoietic recovery the same but BuFlu had a shorter duration of neutropenia and less RBC and Plt transfusion requirements.

González de Villambrosia et al. Haematologica 2008;93(s1):142 Abs.0352

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Cy had better chimerism than Flu

- With follow up of 381 : 160 days (median), outcomes were similar.

Outcome	Cy vs Flu	p-value
Complete donor chimerism Day 30	95% : 40 %	0.0002
Liver toxicity ,HVOD	5% : 5%	
Mortality < D +100	5% (ref aGVHD) : 13% (2 relapse)	
Severe mucositis	55% : 50%	ns
aGVHD Gd III-IV	55% : 25%	0.05
Relapse	15% : 20%	ns

González de Villambrosia et al. Haematologica 2008;93(s1):142 Abs.0352.
HVOD=hepatic veno-occlusive disease

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Could Cy be better in High Risk AML?

- Retrospective review of Cy (48) Vs. Flu (17) for AML CR matched related donor PBSCT or BMT from Dec 1993 to Dec 2009.
- BuCy: Bu PO/IV q6h D -8 to -5 + Cy 60 mg/kg D -3 to -2 OR Flu 30 mg/m^2 D -6 to -3.
- GVHD Proph: Csa + Mtx for 4 doses.
- Cy Vs. Flu: PO Bu 71% : 0%, High risk AML 37% : 94%, PBSCT 58% : 65%, Median follow up 69 : 25 months.

Fedele R, Clin Lym Myel Leuk 2012; 14:6, 493-500.

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Could Cy be better in High Risk AML?

- Mucositis, hepatic, cardiac, pulmonary, hemorrhagic, neurologic, renal toxicities & aGVHD incidence were all similar (ns).
- Nausea worse with Cy (well known with oral Bu)
- Transfusions (median) RBC 2 : 1, Plts 3 : 0
- 2 yr DFS 70% : 59%, EFS 60% : 58%, OS 71% : 63%, OS in high risk 83% : 67% (all p=ns).
- DRM in high risk 11% : 19% p=0.015.

Fedele R, Clin Lym Myel Leuk 2012; 14:6, 493-500.

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Cy is not more toxic

- Retrospective comparison from 1996 to 2012 BuCy2 or BuCy4 (80) vs. FluBu (67), Only IV Bu
- Matched related donor 71.3% : 80.6%, Median Age 36.5 : 46, AML 45% : 62.7%, PBSCT 65% : 100%,
- VOD 16.3% : 7.5% p=0.106
- aGVHD 23.8% : 22.4%
- cGVHD 60% : 77.4% p= 0.03
- 4 Yr survival curves had no significant difference.

Park, S et al. Blood 2012;120(21) Abstract 4522

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Supporting Argument in Favor of BuFlu

- BuFlu is better tolerated than BuCy
- BuFlu demonstrates similar efficacy when compared to BuCy
- BuFlu represents a more convenient dosing regimen than BuCy

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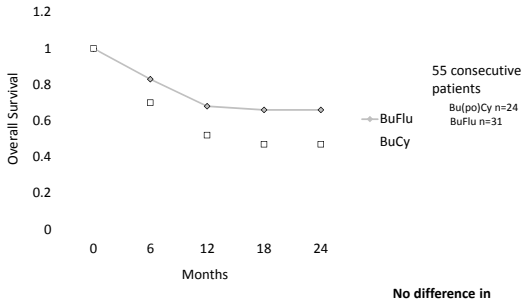
Busulfan IV with Fludarabine



No difference in EFS or OS

Adapted from Altman J, et al. Blood 2006;108:Abstract 2940.

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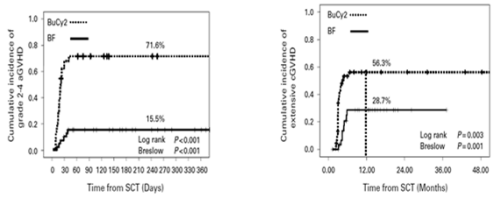
Less GVHD with BuFlu

95 patients (BuFlu n=40; BuCy n=55)



BuFlu regimen resulted in less acute and chronic GVHD and decreased time to engraftment,

Adapted from Chae YS, et al. Bone Marrow Transplant 2007;40:541-7.

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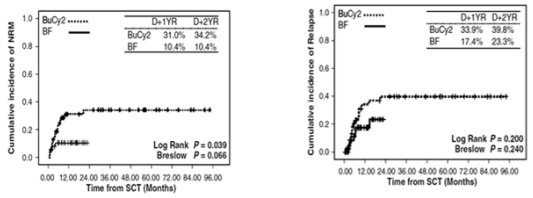
Lower NRM with BuFlu



Adapted from Chae YS, et al. Bone Marrow Transplant 2007;40:541-7.

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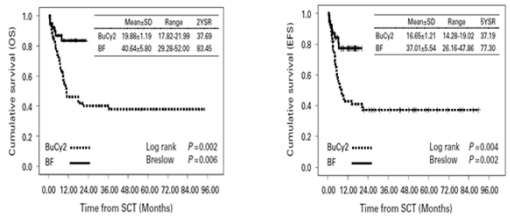
Improved OS and EFS with BuFlu



Adapted from Chae YS, et al. Bone Marrow Transplant 2007;40:541-7.

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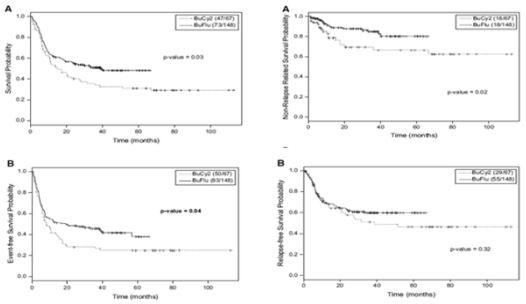
Improved Outcomes with BuFlu

- 215 nonrandomized patients
  - BuFlu n=148
  - BuCy n=67
- BuFlu patients older (46 vs 39 years)
- BuFlu more MUDs (47% vs 21%)

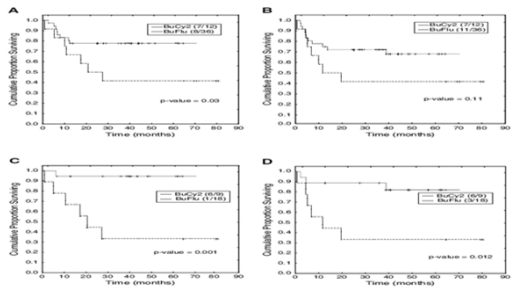
Andersson BS, et al. Biol Blood Marrow Transplant 2008;14:672-84.

Improved OS and EFS with BuFlu



Adapted from Andersson BS, et al. Biol Blood Marrow Transplant 2008;14:672-84.

Improved OS and EFS with BuFlu



A= OS in patients in CR1; B= EFS in patients in CR1
C= OS in patients <= 40 years; D= EFS in patients in CR1

Adapted from Andersson BS, et al. Biol Blood Marrow Transplant 2008;14:672-84.

Similar Efficacy and Reduced Toxicity with BuFlu

- BuFlu vs BuCy (20 patients each, retrospective)
- No difference time to neutrophil or platelet engraftment
  - Duration of neutropenia (ANC <500 uL) shorter in BuFlu group
- Lower red blood cell and platelet transfusion requirements with BuFlu
- No neurological toxicity, GI toxicity, mucositis, liver toxicity, or VOD
- Grade III-IV acute GVHD lower with BuFlu (25% vs 55%, p=.05)
- Day 100 mortality 13% BuFlu (2 relapses) vs 5% BuCy (aGVHD)
- No difference OS 90% BuFlu (med f/u 160 days) vs. 75% BuCy (med f/u 381 days) or relapse rate (20% vs. 15%, respectively)

de Villambrosia SG, et al. Haematologica 2008;93:Abstract 0352.

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BuFlu Similar to BuCy in Efficacy

- CIBMTR prospective cohort study 2009-2011
  - Purpose to compare IV busulfan-containing regimens to TBI-based regimens in patients with myeloid malignancies
  - Subgroup analysis compared BuFlu to BuCy
    - 1025 patients (BuFlu n=424; BuCy n=601)
    - Busulfan PK performed in 56% with dose adjustment done in 78% of those in which it was performed
  - Despite older median age in BuFlu group (49 vs 43 years), outcomes were similar
    - 2-year OS Bu Flu 56% vs. BuCy 57% (p=.79)
    - PFS 50% vs 47%
    - 2-year TRM, relapse, and VOD same

Pasquini M, et al. EBMT 2013 Abstract.
Bredeson C, et al. Blood 2013;122:3871-8.

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BuFlu Similar to BuCy in Efficacy

- Prospective, randomized control trial in 108 patients with AML in 1st CR; median age 30
- Bu 1.6 mg/kg q12h x 4 days with cyclophosphamide 60 mg/kg daily x 2 days or fludarabine 30 mg/m2 daily x 5 days
- No difference chimerism, leukemia relapse, TRM, 5-year DFS or OS
- Regimen-related toxicity lower in BuFlu group
- Grade III-IV acute GVHD higher in BuCy group

Liu H, et al. J Hematol Oncol 2013;6:15-23.

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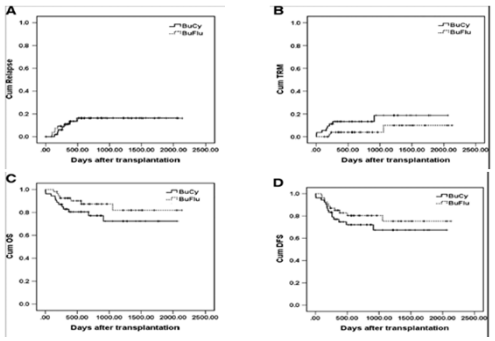
BuFlu Similar to BuCy in Efficacy



Adapted from Liu H, et al. J Hematol Oncol 2013;6:15-23.

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BuFlu Similar to BuCy in Efficacy

- 252 patients randomized to BuCy vs BuFlu
  - Both with IV q6h dosing of busulfan
- AML in 1st or subsequent CR
- Primary endpoint NRM at 1 year

Rambaldi A, et al. Blood 2014; Abstract 727.

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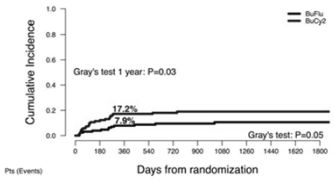
BuFlu Improved NRM Compared to BuCy



Adapted from Rambaldi A, et al. Blood 2014; Abstract 727.

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Less Toxicity with BuFlu

- No difference in relapse, leukemia-free survival, or overall survival compared to BuFlu
- Reduced toxicity with BuFlu
  - Non-relapse death secondary to organ failure 1 vs 9 patients (p=.01)
  - Less acute GVHD and fewer overall toxicities with BuFlu

Rambaldi A, et al. Blood 2014; Abstract 727.

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Meta-Analysis

- No differences in all-cause mortality at 100 days and end of study
- Lower risk of infection and SOS lower in BuFlu group
- Grade 3-4 mucositis comparable between groups
- Lower incidence Grade II-IV acute GVHD with BuFlu[A]

Barouch B, et al. Blood 2014:124:3872.

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Rebuttal-Hutcherson

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Flu = more pneumonia? Modified BuCy

- Randomized Flu (n=52) substituted for Cy (n=53) matched related donor PB/BM for AML, ALL, MDS & CML.
- Modified BuCy: hydroxyurea 40 mg/kg BID D -10 + cytarabine 2 g/m^2 D -9 + Bu 0.8 mg/kg IV q6h D -8 to -6 + Cy 1.8 g/m^2 D -5 & -4 + semustine 250 mg/m^2 PO D -3. Flu arm: 30 mg/m^2 D -5 to -1.
- GVHD proph: Csa/Mtx + MMF D -10 to +14
- Trial suspended: Flu 19.2% (10/52) & Cy 5.7% (3/53) got severe pneumonia. Monitor patients.

Lui, D, et al. Int J Hematol 2013;98:708–715

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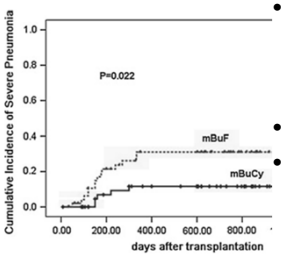
Flu = more pneumonia? Modified BuCy

- Cumulative incidence was Cy 11.6% (5) vs. Flu 31.1% (14). Study permanently terminated.



- 7 of 19 (36.8%) died at median 26 days (16-48) after symptoms of pneumonia.
- Deaths Cy:Flu = 2:5
- Pneumonia mortality was 7% for Cy & 17.5% for Flu. (p=0.125)

Lui, D, et al. Int J Hematol 2013;98:708–715

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RFS: Cy is better than Flu

- Ph III Randomized Trial BuCy (64) vs BuFlu (62) w/o PK monitoring. Median age 41 (17 to 59).
- AML 70 (53 CR1), ALL 47 (42 CR1), MDS 6, CML 2, MDS/MPN 1
- matched related donor/URD Cy 49/15 : Flu 49/13
- Bu IV 3.2 mg/kg Q24h D -7 to -4 + either Cy 60 mg/kg D -3 to -2 or Flu 30 mg/m^2 D -6 to -2.
- GVHD Prophylaxis: Csa/Csa+Mtx; 29/35 : 24/38
- Cy vs Flu: Complete donor chimerism @4 wks 97.2% : 44.4% (p=.001), Graft Failure 0 : 8%.

Lee, JH et al. JCO 2013;31:701-9

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RFS: Cy better than Flu

- Hepatic SOS: 10% : 4.8% p=0.324
- Cy > Flu at 2 yrs:
  - RFS 74.7% : 54.9% p = 0.027
  - OS 67.4% : 41.4% p = 0.014
  - EFS 60.7% : 36.0% p = 0.014
  - NRM 18.7% : 34.4% p = 0.235
- 2 yr OS by Diagnosis
- Myeloid (n= 42 & 37) 68.4% : 42.4% p=0.051
- Lymphoid (n= 22 & 25) 64.2% : 39.5% p=0.068

Lee, JH et al. JCO 2013;31:701-9

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RFS: Cy better than Flu

OS Cy > Flu at 2 yrs:

- Karnofsky ≥ 90 (n= 56 & 49) 68.2% : 46.1% p=0.042
- Karnofsky < 90 (n= 8 & 13) 60% : 32% p=0.213
- Cytogenetics
- Good (n= 46 & 45) 71.5% : 46.2% p=0.038
- Poor (n= 18 & 17) 57.7% : 27 p=0.04
- Matched related donor (n= 49 & 47) 69.4% : 42.8% p=0.19
- URD (n= 15 & 15) 61% : 45.7% p=0.3

Lee, JH et al. JCO 2013;31:701-9

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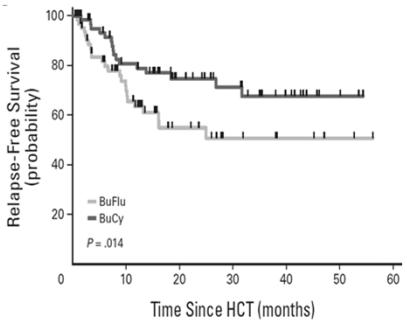
RFS: Cy better than Flu



Lee, JH et al. JCO 2013;31:701-9

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Rebuttal Against BuFlu

- Chae: 41 PO of 55 BuCy. NRM 10% vs 30% matched data for PO vs IV Bu. No pk. Multiple diseases so relapses can't be compared.
- Andersson: non-matched related donor got equine vs. rabbit ATG. Cy was 80% matched related donor vs 50% in Flu. Analysis attempted to account for time difference 1997 to 2001 vs 2001 to 2005.
- Bredeson: >1000 cases of AML, CML or MDS had the same outcomes for overall mortality, TRM, VOD, Relapse and treatment failure.

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Rebuttal Against BuFlu

- Lui, H: Randomized 108 AML CR1 ages 12 to 54. Infections, Overall Survival, Disease Free Survival, TRM and Relapse were similar.
- Rambaldi: Randomized 245 (209 AML w/85% CR1). 1 yr NRM of 17.4% vs. 7.3%. Deaths from organ failures were 9 vs 0 & GVHD 5 vs 3. Trend of more relapse w/ Flu as well as delayed full chimerism.
- Can PK dose adjustments reduce toxicities and possibly relapse in select patients?

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Rebuttal-Engemann

- Nonrandomized trials presented in support of BuCy (Altman, de Villambrosia, Fedele, Park)
  - Retrospective
  - Relatively small numbers
  - Mix of underlying diseases and staging
  - Differences in recipient age and donor type between regimens
  - Many studies presented showed similar efficacy, but with reduced toxicity in favor of BuFlu
    - TRM 17% BuCy vs 0% BuFlu arm (Fedele)

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Rebuttal- Engemann

- Lee study design: phase 3, randomized, controlled trial comparing BuCy and BuFlu
- Small study with 126 patients total; BuFlu arm had more patients with ALL or allele mismatch than BuCy arm
- Both arms received once daily IV busulfan
- No pharmacokinetic analysis or subsequent dosage adjustments performed
- Median age (41 years) lower than in other studies conducted; difficult to extrapolate results to older population
- Despite improvement in OS with BuCy, severe infection (69% vs 50%, p=.032) and gastrointestinal toxicity (upper 31% vs 16%, p=.046; lower 20% vs 8%, p=.073) higher

Lee JH, et al. J Clin Oncol 2013;31:701-9.

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Rebuttal- Engemann

- Two of 3 randomized, controlled trials (Liu and Rambaldi) support the use of BuFlu as an alternative to BuCy with at least similar efficacy and reduced toxicity
- Median age of BuFlu patients in most reports was much higher than in those receiving BuCy
- Regimen-related toxicity lower with BuFlu regimen
- BuFlu is a reasonable alternative to BuCy; especially in older individuals

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ARS Questions

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ARS Question

Do you routinely perform pharmacokinetic analysis on patients receiving q6h IV busulfan?

1. Yes
2. No

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ARS Question

Do you routinely perform pharmacokinetic analysis on patients receiving once daily IV busulfan?

1. Yes
2. No

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ARS Question

What of the following represents the most appropriate target range for once daily busulfan AUC in the BuFlu regimen?

- A. 2000-4000 uMol•min
- B. 4001-6000 uMol•min
- C. 6001-8000 uMol•min
- D. None of the above

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ARS Question

For those using the BuFlu regimen at your center, do you deliver this regimen in the outpatient setting?

A. Always
B. Usually
C. Sometimes
D. Rarely
E. Never

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ARS Question

BuCy and BuFlu are equally efficacious conditioning regimens in patients with myeloid malignancies

1. True
2. False
3. It depends

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ARS Question

Regimen-related toxicity is lower with which of the following when compared to the other?

1. BuCy
2. BuFlu
3. Toxicity is similar

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ARS Question

Which conditioning regimen would you be most likely to recommend for a 40 year old undergoing allogeneic HCT for AML in 1st CR?

1. BuCy
2. BuFlu

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ARS Question

Which conditioning regimen would you be most likely to recommend for a 60 year old undergoing allogeneic HCT for AML in 1st CR?

1. BuCy
2. BuFlu

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Summary

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