Emerging Drugs for HCT Conditioning

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Disclosure

- I have no actual or potential conflicts of interest

Objectives

- Identify emerging agents for stem cell transplant conditioning regimens
- Describe the mechanism of action and impact of these emerging agents on the goals of stem cell transplant conditioning regimens
- Compare common adverse effects of these emerging agents with those of standard therapies
- List dose-limiting toxicities of these emerging agents

Goals of Conditioning Regimens

Eradicate malignancy
- Active against malignancy
- Steep dose response relationship
- Synergy with other agents

Provide immune suppression (Allogeneic HCT)
- Prevent rejection
- Toxic to host T cells

Minimize non-hematologic toxicity
- Reversible toxicity
- Non-overlapping serious toxicities

Baciagalupo A, et al. Biol Blood Marrow Transplant 2009; 15: 1628-33.

Emerging Agents

Clofarabine (Clo)

Bendamustine (Benda)

Gemcitabine (Gem)

Clofarabine

Clofarabine

- 2nd generation adenosine analog
  - Substitution of fluorine at C2′ position of sugar ring
  - Substitution of halogen at 2 position of purine ring
  - More potent than fludarabine or cladribine
- Toxic to both dividing and quiescent lymphocytes
- Food and Drug Administration (FDA) approved
  - Relapsed or refractory acute lymphocytic leukemia (ALL)
  - 52 mg/m^2 daily for 5 days

Zhenchuk A, et al. Biochemical Pharmacology 2009; 78: 1351-59.
Jeha S, et al. J Clin Oncol 2006; 24: 1917-23.
Ewald B, et al. Oncogene 2008; 27: 6522-37.

Mechanism of Action

- Transportation and metabolism
  - Enters cells by passive and facilitated transport
  - Phosphorylated intracellularly to clofarabine monophosphate by deoxycytidine kinase (dCK)
  - Phosphorylated to the active triphosphate form by phosphokinases
  - Incorporated into deoxynucleic acid (DNA)
- Mechanism of anti-cancer activity
  - Inhibition of DNA synthesis and repair
  - Inhibition of ribonucleotide reductase (RR)
  - Direct induction of apoptosis

Zhenchuk A, et al. Biochemical Pharmacology 2009; 78: 1351-59.
Ewald B, et al. Oncogene 2008; 27: 6522-37.

Advantages of Clo

- Improved stability
- Increased intracellular retention
  - Higher affinity for active transporters
  - Higher affinity for dCK (activation)
- Higher affinity for RR and DNA polymerase
- Direct induction of apoptosis
- Less neurotoxicity than fludarabine (Flu)

Zhenchuk A, et al. Biochemical Pharmacology 2009; 78: 1351-59.
Kantarjian H, et al. Leuk Lymphoma 2007; 48(10): 1922-30.
Ewald B, et al. Oncogene 2008; 27: 6522-37.

Toxicity

- Dose limiting toxicities (DLT)
  - Hand-foot syndrome
  - Liver function test (LFT) abnormalities (≥ grade 3)
    - Aspartate aminotransferate (AST) elevation: 38%
    - Alanine aminotransferase (ALT) elevation: 43%
    - Hyperbilirubinemia: 16%
    - Peak at day 7 and reverse within 16 days
- Most common ≥ grade 3: febrile neutropenia, anorexia, hypotension, nausea
- Rare capillary leak syndrome

Jeha S, et al. J Clin Oncol 2006; 24: 1917-23.

Synergistic Activity

- Synergy with alkylating agents
  - Nucleoside analogs inhibit DNA repair enzymes
- Clo 50 times more potent than Flu *in vitro*
- Clo synergizes with Busulfan (Bu) to a greater extent than Flu *in vitro*
- Combination of Flu + Clo had even higher synergistic cytotoxicity with Bu than either alone *in vitro*

Andersson B, et al. Biol Blood Marrow Transplant 2011; 17:893-900.

ARS Question #1

- Unlike Fludarabine, the dose limiting toxicity of clofarabine in HCT conditioning is:

a. Neurologic toxicity
b. Transaminitis
c. Mucositis
d. Veno-occlusive disease

Bu and Clo ± Flu

- Prospective, single center trial
  - Acute myeloid leukemia (AML) or chronic myeloid leukemia (CML)
  - Matched unrelated donor (MUD) or matched related donor (MRD)
- 4 treatment arms
  - Bu 32 mg/m^2 IV test dose
  - MUD recipients: antithymocyte globulin (ATG) 4 mg/kg/course
  - GVHD prophylaxis: mini-methotrexate (MTX) and tacrolimus

Arm	Flu x 4	Clo x 4	Bu (AUC/day) x 4
I	30 mg/m^2	10 mg/m^2	6000
II	20 mg/m^2	20 mg/m^2	6000
III	10 mg/m^2	30 mg/m^2	6000
IV	--	40 mg/m^2	6000

AUC: area under the curve

Andersson B, et al. Biol Blood Marrow Transplant 2011; 17:893-900.

Outcomes

- Engraftment occurred in all patients
  - Neutrophil (median): 12 days (range: 10-22)
  - Platelet (median): 15 days (range: 8-53)
  - Chimerism (median) was 100% at d30 and d100
- Acute graft versus host disease (GVHD)
  - Grade II-IV 31%
  - Grade III-IV 8%
- Median overall survival (OS) was 23 months
- 2yr OS and progression free survival (PFS) 48% and 41%
- Adaptive randomization favored Arm III

Andersson B, et al. Biol Blood Marrow Transplant 2011; 17:893-900.

Toxicity

- Regimen related toxicity
  - Grade II-III mucositis most common (80%)
  - Reversible grade II-III transaminitis (10%)
  - One case of reversible veno-occlusive disease (VOD)
- Treatment related mortality (TRM) 4% at d100 and 15% at 1 yr
  - Infection: 4
  - GVHD: 3

Andersson B, et al. Biol Blood Marrow Transplant 2011; 17:893-900.

Conclusion

- Clo was sufficiently immunosuppressive to promote engraftment
- Active regimen in high risk patients
- Similar toxicity to previous Bu Flu regimen
  - Rates of grade II-III mucositis
  - TRM at 1 yr
  - VOD and transaminitis
- Phase III trial ongoing

Andersson B, et al. Biol Blood Marrow Transplant 2011; 17:893-900.
De Lima, et al. Blood 2004; 857-64.

Phase II: Bu and Clo

- Phase II, single arm
  - Adult patients with ALL
  - MRD or MUD
- Conditioning regimen
  - Clo 40 mg/m^2 daily x 4 days
  - Bu AUC 5500 µMol/min/day x 4 days (AUC 4000 µMol/min/day for age ≥ 60)
  - ATG 4 mg/kg/course for MUD
- GVHD prophylaxis: tacrolimus and mini-MTX
- Primary outcomes: OS and safety

Kebriaei P, et al. Biol Blood Marrow Transplant 2012; 18: 1819-26.

Outcomes

- All patients engrafted
  - 100% donor chimerism in 49% (d30) and 81% (d100)
  - Median time to neutrophil recovery: 11 days
  - Median time to platelet recovery: 14 days
- Acute GVHD: 38% grade II-IV, 12% grade III-IV

	1 year	2 years
OS	67%	50%
Relapse, CR1	16%	37%
Relapse, advanced	37%	46%
Disease free survival (DFS)	54%	35%
Non-relapse mortality (NRM)	32%	43%

Kebriaei P, et al. Biol Blood Marrow Transplant 2012; 18: 1819-26.

Safety

Toxicity	Grade I	Grade II	Grade III	Grade IV
LFT elevations				
Bilirubin*	2(4)	12 (24)	2 (4)	0
ALT	15 (29)	7 (14)	13 (25)	0
Alk phos	9 (18)	1 (2)	0	0
GI tract				
Diarrhea	18 (35)	7 (14)	3 (6)	0
Nausea	19 (37)	30 (59)	1 (2)	0
Mucositis	0	35 (69)	9 (18)	0
Skin rash	9 (18)	4 (8)	1 (2)	1 (2)
Neurologic	3 (6)	3 (6)	0	0
Hypertension	2 (4)	1 (2)	0	0

Graded according to NCI CTCAE v.3
ALT – alanine aminotransferase, Alk phos = alkaline phosphatase, GI = Gastrointestinal
*No cases of veno-occlusive disease (VOD)

Kebriaei P, et al. Biol Blood Marrow Transplant 2012; 18: 1819-26.

Conclusion

- Effective regimen
  - Acceptable engraftment and donor chimerism
  - OS rates in CR1 compare favorably with historical standards
  - Relapse is still main cause of failure
- Comparable safety profile to Bu Flu
  - 6% 100 day mortality
  - Common adverse events (AEs) included reversible transaminitis, nausea, diarrhea and mucositis

Kebriaei P, et al. Biol Blood Marrow Transplant 2012; 18: 1819-26.
De Lima, et al. Blood 2004; 857-64.

Phase I-II: Clo Mel Alemtuzumab

- Single center, prospective trial
  - Patients with advanced hematologic malignancies not suitable for myeloablative conditioning
  - MRD or MUD
- GVHD prophylaxis: tacrolimus

	-7	-6	-5	-4	-3	-2
Alemtuzumab	X	→	→	→	→	
Clo	X	→	→	→	→	
Mel						X

van Besien K, et al. Biol Blood Marrow Transplant 2012; 18: 913-21.

Outcomes

- Engraftment: 100%
  - Neutrophil (median): 10 days
  - Platelets (median): 18 days
  - Full donor chimerism in 98% at d30 (84% full donor T cell)
  - Full donor chimerism declined to 50% by d180
- Acute GVHD: grade II-IV 22%, grade III-IV 5%
- Phase I Maximum Tolerated Dose (MTD):
  - Clo 40 mg/m^2 x 5 and Mel 140 mg/m^2 x 1 with alemtuzumab 20 mg daily x 5 days
  - No DLTs

van Besien K, et al. Biol Blood Marrow Transplant 2012; 18: 913-21.

Phase II Toxicity

	Grade I-II	Grade III-IV	Grade V
Hepatic	58%	39%	
Renal	30%	18%	4% (3 cases)
Skin	8%	9%	

- Renal toxicity
  - Grade II-V was often irreversible
  - Onset occurred within days of starting conditioning
  - Investigators reduced Clo dose and extended infusion
- Hand-foot syndrome occurred in 7 cases
- Severe altered mental status occurred in 4 cases
- Fatal heart failure occurred in 3 cases
- Early fatal shock occurred in 4 cases
  - Occurred during or immediately after completion of conditioning
  - Possibly cytokine release syndrome (hypotension, respiratory distress, multi-organ failure)

van Besien K, et al. Biol Blood Marrow Transplant 2012; 18: 913-21.

Outcomes

	100 days	1 year
TRM	19%	26%
Relapse	--	29%
PFS	60%	45%
OS	80%	59%

- Age > 55 predicted for increased TRM
- Disease risk category was the only significant predictor of PFS
- GFR < 80 mL/min/1.73m^2 on d0
  - Predictor of TRM, OS and relapse
  - Major predictor of long term outcome

van Besien K, et al. Biol Blood Marrow Transplant 2012; 18: 913-21.

Conclusions

- MTD: Clo 40 mg/m^2 x 5 and Mel 140 mg/m^2 x 1 with alemtuzumab 20 mg daily x 5 days
- Clo sufficiently immunosuppressive
  - Potentially more than fludarabine
  - Improved chimerism results compared to previous fludarabine regimen
- Efficacy
  - PFS is similar to previous reports of Flu Mel Alemtuzumab (1 yr PFS 38%)
- Toxicity
  - Unexpected renal toxicity
  - Rare cytokine release syndrome
  - Neurologic toxicity
  - Similar TRM compared to Flu Mel Alemtuzumab (1 yr TRM 33%)

van Besien K, et al. Biol Blood Marrow Transplant 2012; 18: 913-21.
van Besien K, et al. J Clin Oncol 2006; 25: 5728-38.

Other Selected Trials

Author	N	Study Design	Population	Regimen	Outcomes
Khaled S, et al	20	Phase I dose escalation	Leukemia or MDS, high risk	Clo 30-40 mg/m^2 x 5 Mel 100-140 mg/m^2 x 1	-Safe regimen -AEs: hepatic, renal (5), CNS (2), cardiac (1) -OS 77% (1yr) -EFS 71% (1yr)
Krajewski, et al	29	Phase I/II	ALL or AML (MRD, MUD, Cord)	Clo 52 mg/m^2 x 5 Cytarabine 1 gm/m^2 x 6 TBI 12 Gy	-TRM d100 7.6% -Relapse 27% -1yr PFS 52% and OS 46%
Mehta R, et al	17	n/a	Hematologic malignancies (Cord)	Flu 10 mg/m^2 x 4 Clo 30 mg/m^2 x 4 Bu AUC 5000 x 4 TBI 2 Gy x 1	-92% engrafted -TRM d100 < 6% -OS 1yr 88%
Soni S, et al	17	Phase I	Leukemia, pediatric patients (MRD or MUD)	Clo 40-52 mg/m^2 x 5 TBI 2 Gy x 1	-88% full chimerism at d30 -No DLTs -100% engrafted -41% relapsed -58% alive and disease free

Khaled S, et al. Biol Blood Marrow Transplant 2013; 19: Abstract 21.
Krajewski J, et al. Biol Blood Marrow Transplant 2013; 19: Abstract 278.
Mehta R, et al. Clin Lymphoma Myeloma Leuk 2013; [Article in Press].
Soni S, et al. Blood 2013; 122(21): Abstract 3286.

ARS Question #2

Clofarabine satisfies which of the following goals of HCT conditioning regimens for patients with ALL?

a. Active in ALL
b. Provides sufficient immune suppression
c. Minimal non-hematologic toxicities
d. All of the above

Summary of Clo Data

- 2nd generation nucleoside analog
- Evaluated in myeloablative, reduced intensity and non-myeloablative regimens
- Evaluated in pediatric and adult patients
- Toxicity
  - DLTs: reversible transaminitis
  - Unexpected renal toxicity
  - Rare capillary leak syndrome
- Efficacy
  - Favorable results compared to historical controls
  - Phase III trial ongoing

Bendamustine

Bendamustine

- Bifunctional alkylating agent
  - Nitrogen mustard group
  - Benzimidazole ring
  - Butyric acid side chain
- FDA approved:
  - Chronic lymphocytic leukemia (CLL) 100 mg/m^2 d1 and 2 every 28 days
  - Indolent B cell non-hodgkin lymphomas (NHL) 120 mg/m^2 d1 and 2 every 21 days

Tageja N, et al. Cancer Chemother Pharmacol 2010; 66: 413-23.
Cheson B, et al. J Clin Oncol 2009; 27(9): 1492-1501.

Mechanism of Action

- Causes intra and inter-strand cross-links between DNA bases
  - More extensive strand breaks
  - More durable
  - Slower DNA repair
- Unique mechanisms
  - Activate DNA-damage stress response and apoptosis
  - Inhibit mitotic checkpoints
  - Induce mitotic catastrophe
- Incomplete cross-resistance with other alkylators
- Not considered myeloablative

Tageja N, et al. Cancer Chemother Pharmacol 2010; 66: 413-23.

Toxicity

- DLTs from Phase I trials
  - Thrombocytopenia at dose of 180 mg/m^2
  - Cardiac toxicity at dose of 280 mg/m^2

	Phase II NHL		Phase III CLL	
Grade	I-II	III-IV	I-II	III-IV
Neutropenia	26%	58%	4.3%	23%
Thrombocytopenia	62%	25%	13%	11.8%
Lymphopenia	39%	55%	0	6.2%
Anemia	83%	11%	19.2%	2.5%
Infection	42%	19%	4.3%	1.9%
Nausea	71%	4%	18.7%	0.6%
Fatigue	46%	11%	7.5%	1.2%
Infusion reactions/Rash	12% (1 grade IV event)		9.3%	

Cheson B, et al. J Clin Oncol 2009; 27(9): 1492-1501.
Cheson B, et al. Clin Lymph Myeloma and Leukemia 2010; 10(6): 452-7.
Knauf W, et al. J Clin Oncol 2009; 27: 4378-84.

Phase II: FBR

- Expanded Phase II trial
  - Lymphoid malignancies
  - MRD or MUD
- GVHD prophylaxis: Tacrolimus and mini-MTX

	D-13	D-6	D-5	D-4	D-3	D-2	D-1	D0	D+1	D+8
Flu 30 mg/m^2			→	→	→					
Benda 130 mg/m^2			→	→	→					
Rituximab mg/m^2	375	1000							1000	1000
ATG* 1 mg/kg						→	→			

*ATG for recipients of MUD only

Khouri I, et al. Blood 2013; 122(21): Abstract 541.

Demographics

	N = 56
Age, median	56 (range: 59-70)
Histology	
Mantle cell	16 (29%)
Chronic lymphocytic leukemia (CLL)	15 (27%)
Follicular	13 (23%)
Diffuse large B cell	9 (16%)
Peripheral T cell	3 (5%)
Median prior treatments	3
Prior autologous transplant	7 (13%)
Disease status	
CR/CRu	27 (48%)
Partial response (PR)	23 (41%)
Refractory	6 (11%)
Donor	
MUD	30 (54%)
MRD	26 (54%)

Khouri I, et al. Blood 2013; 122(21): Abstract 541.

Outcomes

- Engraftment
  - Neutrophil: 6 days (range: 0-16 days)
    - Median days on filgrastim: 1.5
    - 23% did not require filgrastim
  - Platelet: 11 days (range; 10-19)
    - 87.5% did not require platelet transfusions
- Chimerism
  - Median d30: 85% myeloid and 97% T cells
  - Increased to 100% by d90
- Acute GVHD grade II-IV: 12.5%
- Chronic GVHD (extensive): 14%

Khouri I, et al. Blood 2013; 122(21): Abstract 541.

Outcomes

- TRM at 1 yr was 9%
  - 6 deaths
  - Cause of death (2 each): GVHD, infection and progression
- Median follow-up 12 months
- OS 89%
- PFS 80%

Khouri I, et al. Blood 2013; 122(21): Abstract 541.

Conclusion

- Very well tolerated regimen
  - Minimal hematologic toxicity
  - Low TRM
  - Feasible in older population
  - Acceptable engraftment
- Similar toxicity to previous reports for FCR (fludarabine cyclophosphamide rituximab)
- Potentially suitable for outpatient alloHCT

Khouri I, et al. Blood 2013; 122(21): Abstract 541.
Khouri I, et al. Experimental Hematology 2004; 32: 28-36.

Phase I: Benda and Mel

- Phase I, dose escalation trial
- Multiple myeloma patients eligible for AutoHCT
- Regimen
  - Mel 100 mg/m^2 on d-2 and d-1
  - Bendamustine dose escalation

Dose Cohort	d-2	d-1
1		30 mg/m^2
2		60 mg/m^2
3		90 mg/m^2
4	60 mg/m^2	60 mg/m^2
5	90 mg/m^2	60 mg/m^2
6	125 mg/m^2	100 mg/m^2

Mark T, et al. Biol Blood Marrow Transplant 2013; 19: 831-7.

Demographics

	N = 25
Age, median	56 (range: 37-65)
Intermediate-High risk disease by Durie-Salmon International Staging System	 75% 55%
High risk cytogenetics	28%
Disease Status at time of HCT sCR CR VGPR PR PD	 20% 20% 32% 24% 4%

sCR: stringent CR; VGPR: very good partial response; PD: progressive disease

Mark T, et al. Biol Blood Marrow Transplant 2013; 19: 831-7.

Outcomes

- Engraftment
  - Neutrophil: 11 days (range: 9-14 days)
  - Platelet: 13 days (range: 11-21 days)
- Overall response rate (ORR) 79% at d100
- Median PFS 26.4 months
- Median OS was not reached, actuarial 2 yr OS 70%
- 6 patients died during the study, all from progressive myeloma

Mark T, et al. Biol Blood Marrow Transplant 2013; 19: 831-7.

Toxicity

- TRM 0% at d100
- DLT: respiratory failure occurred in 1 patient
- No cardiac events attributed to benda

	Grade I-II	Grade III	Grade IV
Mucositis	85%	8%	
Diarrhea	84%	4%	
Nausea/vomiting	88%		
Anorexia	64%		
Fever	52%		
Sepsis			4% (1 patient)
Dyspnea	20%		4% (1 patient)
Fatigue	72%		
Rash	25%		

Mark T, et al. Biol Blood Marrow Transplant 2013; 19: 831-7.

Conclusions

- MTD was not reached
- Safe combination
  - Similar mucositis rates to Mel alone
  - 1 DLT was not attributed to benda
  - No cardiac toxicity observed
- Not designed to assess efficacy

Mark T, et al. Biol Blood Marrow Transplant 2013; 19: 831-7.

Phase I-II: BeEAM

- Phase I-II, dose escalation trial
  - Benda replaces carmustine in BEAM for AutoHCT
  - Relapsed/resistant non-hodgkin lymphoma (NHL) or hodgkin lymphoma (HL)

	d-7	d-6	d-5	d-4	d-3	d-2	d-1
Benda 1: 160 mg/m^2/day 2: 180 mg/m^2/day 3: 200 mg/m^2/day	→	→					
Cytarabine 400 mg/m^2/day			→	→	→	→	
Etoposide 200 mg/m^2/day			→	→	→	→	
Mel 140 mg/m^2/day							→

Visani G, et al. Blood 2011; 118(12): 3419-25.

Demographics

	N = 43
Age, median	47 (range: 18-70)
Disease HL NHL	 15 (35%) 28 (65%)
Median lines of previous therapy	2 (range: 2-5)
Disease status at enrollment Primary refractory Relapse	 21 (49%) 22 (51%)
Disease status at HCT CR2 or beyond Partial response No response/progression	 16 (37%) 20 (46%) 7 (17%)

Visani G, et al. Blood 2011; 118(12): 3419-25.

Outcomes

- Engraftment
  - Neutrophil: 10 days (range: 8-12 days)
  - Platelet: 13 days (range: 8-39 days)
- Safety
  - No DLTs in Phase I
  - TRM 0% at d100
- Regimen related toxicity
  - Elevated LFTs: 44%
  - Mucositis (grade III-IV): 26%
  - Gastroenteritis (grade II-III): 35%
  - Mild nausea/vomiting
  - Fever: 51% (1 documented fungal infection)

Visani G, et al. Blood 2011; 118(12): 3419-25.

Outcomes

- 81% alive and disease free at 18 months
- Greater probability of being disease free
  - Chemosensitive
  - NHL
- Median DFS
  - HL: 19 months
  - NHL: not reached
- 50% PET+ patients became negative after HCT
- Relapse in 14%
  - Median 3 months post-HCT
  - 2 patients died

Visani G, et al. Blood 2011; 118(12): 3419-25.

Conclusions

- Acceptable safety profile
  - No DLT
  - No cases of pneumonitis, dose-limiting cardiac toxicity or VOD
  - Low TRM
  - Similar toxicity compared to previous reports of BEAM
- Effective regimen compared to historical data
- Further studies are planned

Visani G, et al. Blood 2011; 118(12): 3419-25.
Argiris a, et al. Ann Oncol 2000; 11: 665-72.
Puig N, et al. Leuk Lymphoma 2006; 47(8): 1488-94.

ARS Question #3

The addition of bendamustine to melphalan did not appear to increase rates of mucositis compared to melphalan alone.

a. True
b. False

Bendamustine Conclusions

- Current data
  - Included in regimens for auto and allo HCT
  - Lymphoid malignancies and myeloma
  - *In vitro* data supporting synergy with other agents
- Safety
  - Minimal non hematologic toxicity
  - Low TRM
- Efficacy
  - Favorable outcomes
  - No direct comparison with current standards

Gemcitabine

Gemcitabine

- Deoxycytidine analog
- Synergy with alkylating agents through inhibition of DNA repair
- Limited extramedullary toxicity at standard doses
- FDA approved
  - Pancreatic, breast, non-small cell lung and ovarian cancers
  - Dose range: 1000-1250 mg/m^2

Nieto Y, et al. Biol Blood Marrow Transplant 2012; 18: 1677-86.

Mechanism of Action

- Activation of gemcitabine
  - Phosphorylated by dCK to monophosphate
  - Further phosphorylation by other phosphokinases to active triphosphate
- Anti-cancer activity
  - Incorporated into DNA and inhibits DNA polymerases leading to chain termination
  - Inhibits DNA repair enzymes
  - Inhibits RR

Guchelaar H, et al. Cancer Treatment Reviews 1996; 22: 15-31.

Fixed Dose Rate (FDR) Infusions

- Rate limiting step in activation is phosphorylation by dCK
  - Saturated at Gem concentrations above 20 µmol/L
  - Maximal activation of Gem occurs when concentrations are 10-20 µmol/L
  - FDR infusion of Gem 8-10 mg/m^2/min achieves the target concentration
- Standard infusion time is 30 minutes
  - Cells are unable to activate a large portion of Gem
  - Possible inhibition of dCK

Gandhi V, et al. J Clin Oncol 2002; 20: 665-73.
Brand R, et al. Investigational New Drugs 1997; 15: 331-341.

Comparison to Cytarabine

- More potent inhibitor of DNA synthesis
- Higher intracellular accumulation of triphosphate
  - Faster membrane transport
  - Greater effectiveness of dCK for activating gemcitabine
  - Longer retention of triphosphate

Guchelaar H, et al. Cancer Treatment Reviews 1996; 22: 15-31.

Toxicity

- Myelosuppression considered DLT at standard doses
  - More severe in FDR infusions
- Common non-hematologic toxicities
  - Nausea/vomiting
  - Mild skin rash
  - Fever and flu-like syndrome
  - Elevated LFTs

Guchelaar H, et al. Cancer Treatment Reviews 1996; 22: 15-31.
Burris H, et al. J Clin Oncol 1997; 15: 2403-13.
Noble S, et al. Drugs 1997; 54(3): 447-72.
Brand R, et al. Investigational New Drugs 1997; 15: 331-41.

Gem Bu Mel

- Phase I-II, single center, dose escalation trial
- Refractory/relapsed lymphoma or myeloma
- Eligible for first AutoHCT
- Rationale for addition of Gem to Bu Mel
  - Synergy with alkylating agents
  - Efficacy in lymphoma
  - Minimal non hematologic toxicity
  - *In vitro* studies demonstrated superior activity of 3 drug combination over 2 drug combinations

Nieto Y, et al. Biol Blood Marrow Transplant 2012; 18: 1677-86.

Gem Bu Mel Regimen

	d-10	d-9	d-8	d-7	d-6	d-5	d-4	d-3	d-2	d-1	0	d+1	d+2
Gem 225-2775 mg/m^2/day Daily 3 dose 2 dose			 X X X	X	 X X	X		 X X X	X				
Bu AUC 4000 µMol/min	test		X	X	X	X							
Mel 60 mg/m^2/day								X	X				
Rituximab (CD20+) 375 mg/m^2												X	X

- Gem infused at FDR of 10 mg/m^2/min after 75 mg/m^2 bolus
- Supportive care
  - Palifermin, cryotherapy, glutamine and caphosol (®) for mucositis prevention
  - Filgrastim starting on d+5

Nieto Y, et al. Biol Blood Marrow Transplant 2012; 18: 1677-86.

Demographics

	N = 133
Age, median	41 (range: 18-65)
Disease HL NHL Myeloma	 80 46 7
# Prior regimens, median	3 (range: 2-9)
Prior radiation	32
Disease status CR PR PD PET positive (HL and NHL)	 60 (45%) 34 (26%) 39 (29%) 64/126 (50%)

Nieto Y, et al. Biol Blood Marrow Transplant 2012; 18: 1677-86.

Regimen Related Toxicity

- Daily and 3 dose schedule excessive toxicity
- 2 dose schedule less toxic
  - Gem MTD 2775 mg/m^2/dose
  - Mucositis was DLT
    - Started median d+4
    - Persisted for 2 days at maximum severity
    - 65% required narcotic PCA for median 6 days
  - Rash (grade I-II) common
  - Reversible transaminitis common (75%)
    - Start at median d+1 and resolve in 1 week
    - No cases of VOD
    - Mild bilirubin elevations in 11%
  - Pulmonary: 2 cases pneumonitis (grade II) in patients who received prior radiation
- 2 patients died from infection

Nieto Y, et al. Biol Blood Marrow Transplant 2012; 18: 1677-86.

Outcomes

HL (n = 80)
- CR 62% and response rate (RR) 88% (measurable disease)
- EFS 54% and OS 72%
- 37 (46%) relapsed and 20 died

NHL (n = 46)
- CR 88% and RR 96% (measurable disease)
- EFS 60% (B cell) and 55% (T cell)
- 25 alive and in CR
- All 3 Burkitt's relapsed and died

Myeloma (n = 7)
- CR 57% and RR 71%
- 4 relapsed and died from progression

Nieto Y, et al. Biol Blood Marrow Transplant 2012; 18: 1677-86.

Conclusions

- Gem MTD 2775 mg/m^2/dose for 2 doses
- Toxicity
  - Mucositis was DLT
  - Rash and reversible transaminitis were common
  - More toxic than previously reported Bu Mel regimen
- Efficacy
  - Favorable results compared to historical data in high risk populations
  - No conclusion in myeloma due to small number of patients

Nieto Y, et al. Biol Blood Marrow Transplant 2012; 18: 1677-86.
Kebriaei P, et al. Biol Blood Marrow Transplant 2011; 17(3): 412-20.

Comparison of Regimens for HL

- Poor risk or refractory HL patients undergoing AutoHCT
- Described 3 separate cohorts

BEAM	• Carmustine 300 mg/m^2 daily x 1 • Etoposide 200 mg/m^2 Q12 x 4 days • Cytarabine 200 mg/m^2 Q12 x 4 days • Mel 140 mg/m^2 daily x 1
Bu Mel	• Bu AUC 5000 µMol/min daily x 4 days • Mel 70 mg/m^2 daily x 2 days
Gem Bu Mel	• Gem 2775 mg/m^2 daily x 2 • Bu AUC 4000 µMol/min daily x 4 • Mel 60 mg/m^2 daily x 2

Nieto Y, et al. Biol Blood Marrow Transplant 2013; 19: 410-7.

Demographics

	BEAM (N = 57)	Bu Mel (N = 39)	Gem Bu Mel (N = 84)	P-value
Age, median	36 (20-63)	31 (17-69)	32 (19-61)	0.7
Primary refractory disease	40%	31%	61%	0.001
First remission duration 3-6 months 6-12 months >12 months	 82% 13% 5%	 75% 10% 15%	 83% 5% 12%	0.2
Bulky tumor at relapse	24%	20%	38%	0.03
Salvage regimens > 1	39%	49%	44%	0.6
PET+ at transplant	27%	28%	51%	0.001
Tumor growth at transplant	3%	6%	26%	< 0.0001
Prior radiation	30%	30%	27%	0.9
Post-transplant radiation	9%	21%	26%	0.02

Nieto Y, et al. Biol Blood Marrow Transplant 2013; 19: 410-7.

Outcomes

	BEAM	Bu Mel	Gem Bu Mel	P-value
EFS	39%	33%	57%	NR
EFS (combined)	35%		57%	0.01
OS	59%	52%	82%	NR
OS (combined)	54%		82%	0.04

- No difference in outcome BEAM vs Bu Mel
- Independent variables for worse EFS
  - Regimen other than Gem Bu Mel
  - PET positive
  - # salvage therapies
- Independent variable for worse OS
  - Regimen other than Gem Bu Mel
  - PET positive

Nieto Y, et al. Biol Blood Marrow Transplant 2013; 19: 410-7.

Conclusions

- Efficacy
  - Improved outcome with Gem Bu Mel (EFS and OS) despite poor prognostic features
- Limitations
  - No patient received brentuximab
  - Not randomized
  - Limited toxicity data reported
  - Different median follow up times

Nieto Y, et al. Biol Blood Marrow Transplant 2013; 19: 410-7.

Other Selected Trials

Author	N	Study Design	Population	Intervention	Outcomes
Anderlini P, et al	15	Single arm, prospective	• Relapsed HL (non-progressive) • Adults • MRD or MUD	Gem 800 mg/m^2 d-7 Flu 33 mg/m^2 d-5 → d-2 Mel 70 mg/m^2 d-3 → d-2 ATG 4 mg/kg for MUD	• 1 graft failure • 100% donor (13/13) • d100 TRM 13% • OS 87% and PFS 49% at 18 mo
Nieto Y, et al	52	Phase I, dose escalation	• Relapsed or refractory solid tumors and lymphomas • AutoHCT	Gem FDR d-6 D 300-350 mg/m^2 d-5 Mel 50 mg/m^2 d-3→d-1 C 333 mg/m^2 d-3→d-1	• Gem MTD 12000 mg/m^2 • DLT enteritis • CR 50% • 2yr OS 79%, EFS 49%
Arai S, et al	92	Phase I/II, dose escalation	• Relapsed or refractory HL • Adults • AutoHCT	Gem d-13 & d-8 V 30 mg/m^2 d-13 & d-8 BCNU 10 mg/kg d-6 E 60 mg/kg d-4 Cy 100 mg/kg d-3	• Gem MTD 1250 mg/m2 • Early TRM 3% • BCNU toxicity 15% • 2yr OS 83%, EFS 67% • 2yr NRM 6%

D = docetaxel; C = carboplatin; V = vinorelbine; E = etoposide; Cy = cyclophosphamide; BCNU = carmustine

Anderlini P, et al. Leuk Lymphoma 2012; 53(3): 499-503.
Nieto Y, et al. Biol Blood Marrow Transplant 2007; 13: 1324-37.
Arai S, et al. Biol Blood Marrow Transplant 2010; 16(8): 1145-54.

Gem Conclusion

- Efficacy
  - In vitro data supports synergy with alkylating agents
  - Gem Bu Mel combination may provide improved outcomes in HL patients
- Safety
  - DLT: mucositis
  - Increased rates of toxicity compared to Bu Mel, but mostly reversible
  - Common toxicities: skin, transaminitis

ARS Question #4

The dose limiting toxicity of gemcitabine in combination with busulfan and melphalan is

a. Veno-occlusive disease
b. Pulmonary fibrosis
c. Mucositis
d. Cutaneous reactions

Other Emerging Agents

- Ibritumomab Tiuxetan
  - Radioimmunoconjugate targeting CD20
- Ofatumumab
  - Fully human monoclonal antibody targeting CD20
- Vorinostat
  - Histone deacetylase inhibitor
- Azacitidine
  - Hypomethylating agent
- Brentuximab vedotin
  - Antibody drug conjugate targeting CD30

Conclusions

- Current data
  - Majority are single arm trials
  - Comparison to historical data
- DLT in conditioning regimens
  - Clo: transaminitis
  - Benda: none identified at current doses in HCT
  - Gem: mucositis
- Further study is ongoing to determine comparative efficacy