THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Azacitidine/Vorinostat/GemBuMel with Autologous SCT in Patients with Refractory Lymphomas
2013-0186

Core Protocol Information

Short Title	Aza-SAHA-GBM with AutoSCT for Refractory Lymphoma
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Full Title:	Azacitidine/Vorinostat/GemBuMel with Autologous SCT in Patients with Refractory Lymphomas
Protocol Type:	Standard Protocol
Protocol Phase:	Phase I/Phase II
Version Status:	Terminated 11/22/2017
Version:	08
Submitted by:	Peggy S. LeCompte--2/24/2015 2:19:16 PM
OPR Action:	Accepted by: Yolanda Shorte -- 3/11/2015 11:02:34 AM

Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

Primary Endpoints

1. To determine the recommended dose of azacitidine in combination with vorinostat/ Gemcitabine/Busulfan/Melphalan.
2. To determine the event-free survival (EFS) in the population of patients enrolled.

Secondary endpoints

1. To determine the overall survival (OS) of these patients.
2. To determine the response and complete response rates of this regimen.
3. To describe the toxicity profile of this treatment.

2.0 Background

More active high-dose chemotherapy regimens are needed for patients with refractory lymphoid tumors receiving an autologous stem-cell transplant (ASCT). To this end we are developing new and hopefully better regimens through a series of sequential trials following an epigenetic-modulated alkylator/nucleoside analog paradigm. Such regimens have included busulfan/melphalan, gemcitabine/busulfan/melphalan and vorinostat/gemcitabine/busulfan/melphalan.

2.1. Busulfan/Melphalan (BuMel)

DNA-targeting alkylating agents form the backbone of most hematopoietic cell transplantation regimens based on their log-linear increases in tumor killing with increasing dose. The cytotoxic principle is believed to be DNA damage produced by direct linking to individual bases and cross-linking of the complementary DNA strands.

We developed a high-dose regimen of pharmacokinetically dose-adjusted intravenous busulfan combined with melphalan (BuMel, protocol 2004-0190), which was well tolerated with minimal hepatic toxicity (1 case of mild venoocclusive disease among 102 patients enrolled),[1] in contrast to earlier versions of this regimen. Thus, we considered BuMel a safe alkylator-based platform for our subsequent studies.

2.2. Gemcitabine/Busulfan/Melphalan (GemBuMel)

Critical factors modulating alkylating agent activity are the extent of DNA damage and repair. Thus, combined use of alkylating agents and drugs known to inhibit DNA repair, such as the nucleoside analogue gemcitabine, produces additive or synergistic effects. To exploit their synergy, we combined high-dose gemcitabine with BuMel (GemBuMel) (protocol 2006-0803), based on the following principles:

1. Individual activity of the three drugs against lymphoid tumors.
2. Synergy between gemcitabine and the alkylating agents, based on inhibition of DNA damage repair.
3. Improved antitumor activity of gemcitabine when administered at a prolonged fixed dose (FDR) compared to shorter infusions. Gemcitabine is activated by intracellular phosphorylation by deoxycitidine kinase (dCK), a rate-limited process. Previous studies had shown that an extracellular gemcitabine concentration below 20 micromolar resulted in

optimal gemcitabine incorporation into DNA, and that higher concentrations saturated dCK. A FDR of 10 mg/m2/min avoids saturation of dCK[2] and increases the antitumor activity and myelotoxicity of gemcitabine. The latter result is easily overcome in the transplant setting with stem-cell support.

4. Minimal overlapping extramedullary toxicity of the three agents.
5. Optimization of busulfan therapy by therapeutic drug monitoring.

In this dose- and schedule-finding trial we administered gemcitabine as a loading dose of 75 mg/m2 (calculated to reach a steady state concentration of 15 micromolar), followed by a continuous infusion at 10 mg/m2/min.[3] The length of infusion of gemcitabine was escalated in successive cohorts. We enrolled 133 patients with refractory lymphoid tumors receiving an autologous transplant, including 80 with Hodgkin's lymphoma (HL) and 46 with non-Hodgkin's lymphoma (NHL). The optimal schedule was determined to be two doses of gemcitabine, one before each of the first doses of busulfan and melphalan. The optimal length of infusion of gemcitabine, following its loading dose, was established at 4.5 hours.

Table 1. GemBuMel schedule

Day	-8	-7	-6	-5	-4	-3	-2	-1	0
Gemcitabine 75 mg/m2 followed by 4.5-hr CI at 10 mg/m2/min	X					X			
Busulfan (target AUC: 4,000 microM.min/day)	X	X	X	X					
Melphalan 60 mg/m2/day						X	X		
PBPC infusion									X

Toxicity Profile of GemBuMel

At its MTD GemBuMel caused reversible mucositis (60% grade 2, 13% grade 3), skin toxicity (13% grade 2) and self-limited elevation of the transaminases (21% grade 2, 7% grade 3), with no grade 4 or 5 toxicities.

Antitumor Activity of GemBuMel.

GemBuMel was highly active in all lymphoid diagnoses. The EFS and OS rates of patients with refractory HL were 61% and 94%, respectively, at current median follow-up of 24 (range, 3-50) months. These results compare favorably with those observed in two separate contemporaneous cohorts of refractory HL patients treated at our department since January 2005 with BEAM (N=79) or BuMel (N=38).[4]

All of these patients met eligibility criteria for 2006-0803 but either received BEAM off protocol or were enrolled in the phase II trial of BuMel (2004-0190). The GemBuMel cohort had significantly worse prognostic features than the BEAM or BuMel groups, specifically a higher prevalence of PET-positive disease at the time of HDC, extranodal disease at the time of relapse and a higher number of prior relapses. In spite of its worse prognostic features, the

GemBuMel group had significantly better EFS and OS than the BEAM or BuMel groups (Fig. 1).

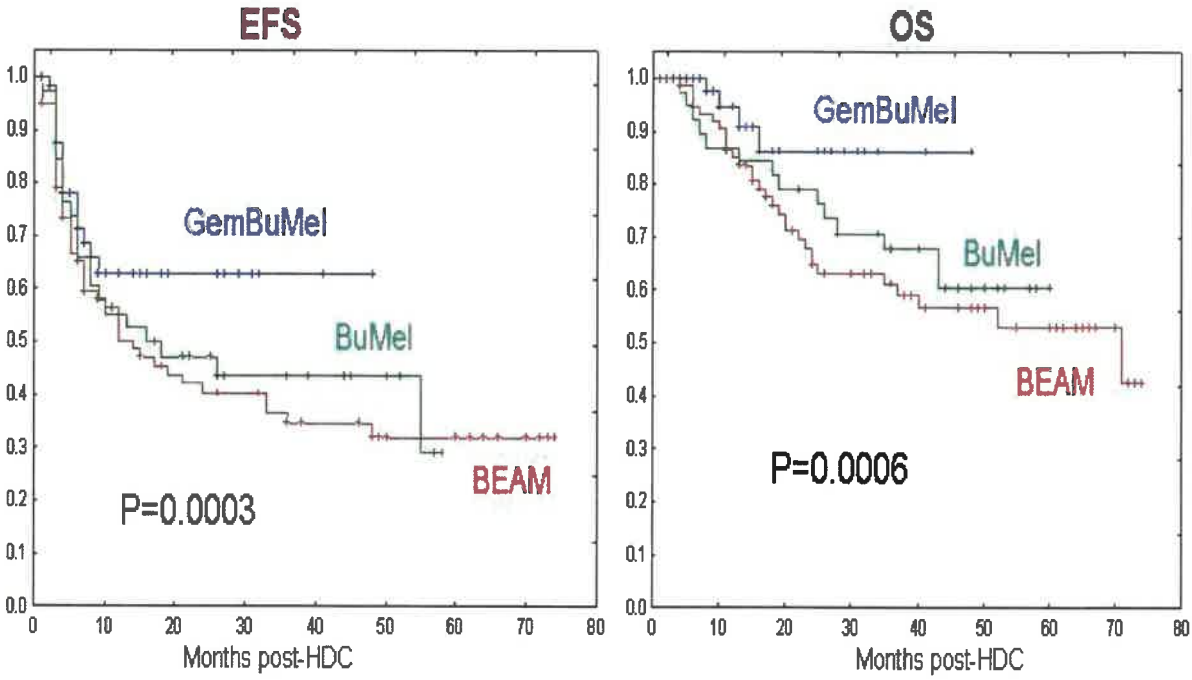

Fig 1. Comparison of GemBuMel, BEAM and BuMel in all patients with refractory HD treated since 1/2005.

With respect to NHL, 34 patients with large B-cell lymphoma (N=19), T-cell lymphoma (N=10), Burkitt's lymphoma (N=4) and marginal zone lymphoma (N=1) were enrolled in the GemBuMel trial. These patients were pretreated with a median 3 prior chemotherapy regimens, had a median IPI at relapse of 3, 2 prior relapses, and 62% of them had PET-positive disease at the time of HDC. In this refractory population the RR and CR rates were 92% and 77%, respectively. At present median follow-up of 12 (1-40) months, the EFS and OS rates are 61% and 67%, respectively.

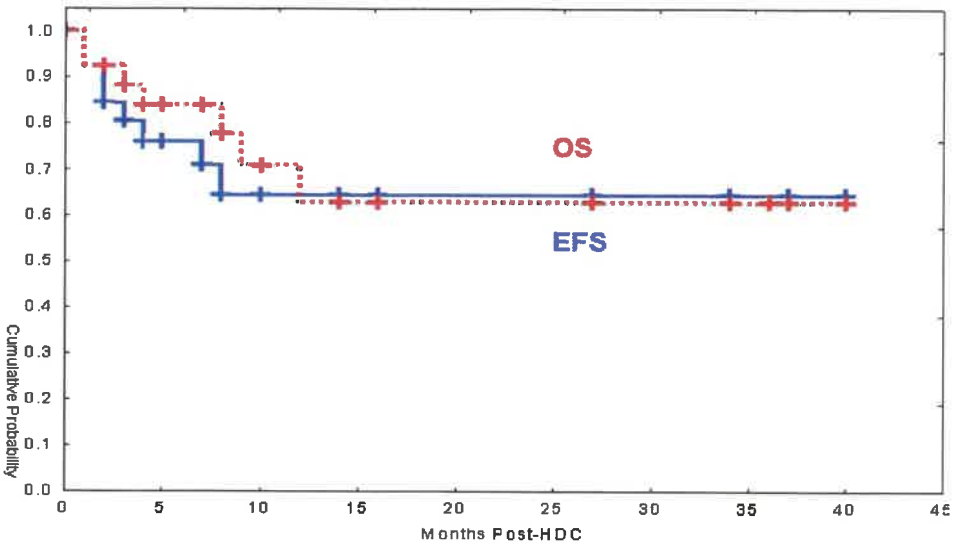

Fig 2. EFS/OS of NHL pts receiving GemBuMel.

2.3. SAHA/GemBuMel

Another factor affecting the activity of alkylating agents is their access to DNA, which largely depends on the configuration of chromatin. Acetylation of lysine residues in the histones leads to charge neutralization, decreased binding to the DNA backbone, changes in the conformation of DNA and gene expression, and relaxation of chromatin. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) add and remove acetyl groups, respectively. Addition of acetyl groups by HATs or inhibition of HDACs results in the weakening of the bond between histones and DNA, increasing gene transcription and decondensing chromatin.

Vorinostat is an inhibitor of all classes of HDACs that induces cell cycle arrest, differentiation and apoptosis. This drug is the only HDAC inhibitor currently approved by the FDA. Some activity has been seen in patients with relapsed Hodgkin's lymphoma,[5] diffuse large B-cell lymphoma,[6] and indolent B-cell NHL.[7] Single-agent vorinostat appears to be particularly active in T-cell lymphoma, more specifically in cutaneous T-cell lymphomas, with response rates of 25-30%.[8,9]

The duration of vorinostat-induced histone hyperacetylation is directly proportional to its dose.[10] The side effects of daily or twice daily vorinostat administered over prolonged periods of time include myelosuppression, fatigue, diarrhea, nausea and muscle spasms. Only rarely has it been shown to prolong the QT interval.

An alternative (and perhaps more effective) use to single-agent long-term administration of vorinostat, is its combination with DNA-targeting agents. Vorinostat induces relaxation and decondensation of the chromatin, rendering the DNA more accessible to DNA-targeting agents such as alkylators and nucleoside analogues. Preclinical experiments by our collaborators Valdez and Andersson have shown striking synergy, determined by apoptosis or survival readouts, when vorinostat was added to GemBuMel (all drugs present at clinically achievable levels), in lymphoma B-cell (Daudi) and T-cell (J45) lines, which were resistant to those agents

when exposed to them separately. The optimal schedule of the combination of SAHA with GemBuMel was determined to be simultaneous SAHA/GemBuMel exposure, superior to sequential SAHA -> GemBuMel or GemBuMel -> SAHA. Lymphoma cells exposed to SAHA/gemcitabine/busulfan/melphalan experienced increased cleavage of PARP1 and increase in gamma-H2AX, reflecting increased DNA damage response.

These observations led to our phase 1 clinical trial 2011-0407 to evaluate a short schedule of vorinostat combined with GemBuMel with autologous stem cell support. We have gradually escalated the dose of vorinostat starting at 200 mg daily, with the MTD of SAHA identified at 700 mg daily. There have been no regimen-related deaths and the toxicity profile appears comparable to that previously observed with GemBuMel alone. We have not seen significant prolongations of QT before and after treatment.

We have enrolled 48 patients to date (13 HL, 35 DLCL).

2.4. Azacitidine/SAHA/GemBuMel

Experiments by Valdez and Andersson suggest that the ability of SAHA to sensitize cells to DNA-damaging agents through chromatin remodeling may still not be maximized.[11] Following exposure of lymphoma cell lines to SAHA/GemBuMel, increased protein levels of DNA methyltransferases 3A and 3B were detected by Western Blot (Fig. 3-A). The induction of DNMT3A and DNMT3B peaked at approximately 48 hours following drug exposure (Fig. 3-B). The induction of DNMT3A and DNMT3B was associated with an increase in global DNA methylation as indicated by an increase in global 5-methylcytidine (Fig. 3-C).

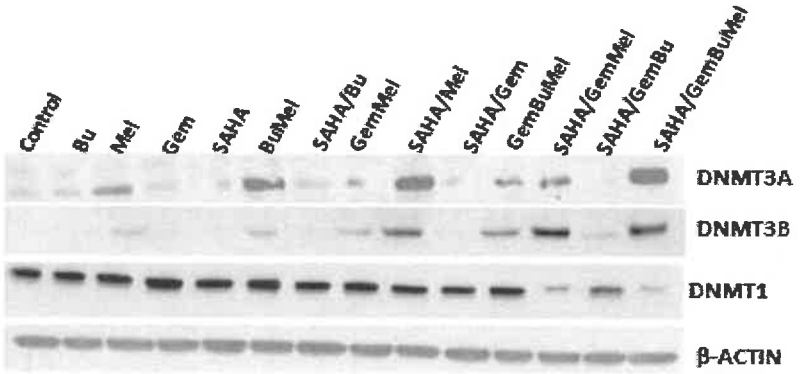

Fig. 3-A. Expression of DNA methyltransferases after various combinations of SAHA/GemBuMel.

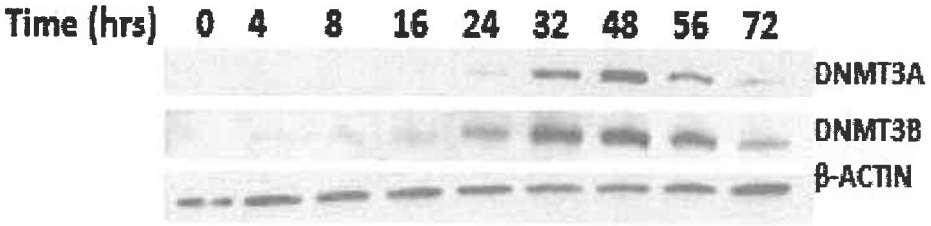

Fig. 3-B. Time-related expression of DNA methyltransferases after SAHA/GemBuMel.

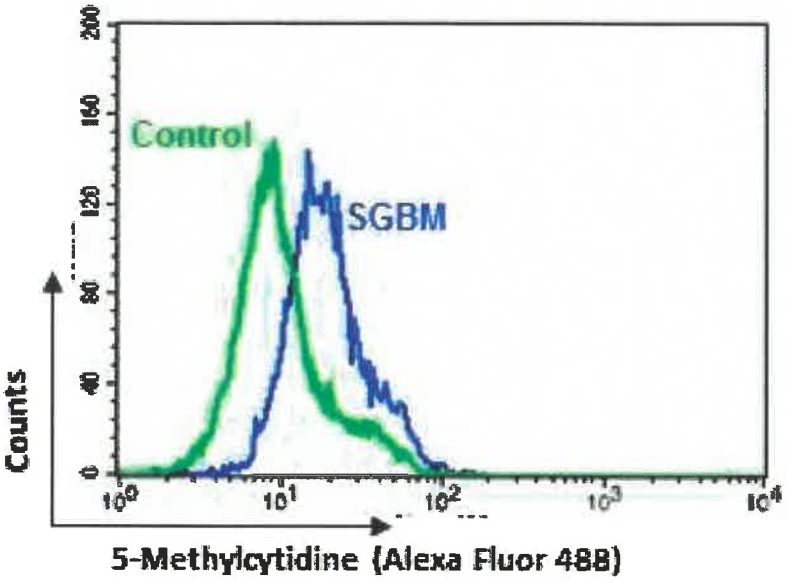

Fig. 3-C. Increased global DNA methylation after SAHA/GemBuMel.

These observations suggested that inhibition of DNA methyltransferases could further enhance the cytotoxicity of SAHA/GemBuMel. Addition of azacitidine to SAHA-GemBuMel abrogated the induction of DNMT3A and DNMT3B and had a profound effect on cytotoxicity (Fig. 4-A). A 50% decrease in cell proliferation of refractory Daudi cells was observed with SAHA/GemBuMel compared to control, with further decrease to less than 15% with azacitidine/SAHA/GemBuMel (Fig. 4-B). Cell cycle analysis showed that sub-G1 DNA content increased from 28% (SAHA/GemBuMel) to 62% (azacitidine/SAHA/GemBuMel), indicating increased activation of apoptosis (Fig. 4-B). Likewise, the enzymatic activities of caspases 3 and 9 were substantially increased in cells exposed to aza/SAHA/GemBuMel (Fig. 4-C).

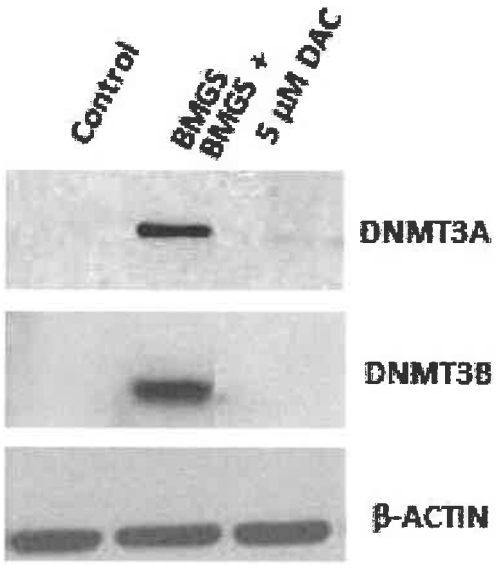

Fig. 4-A. Abrogation of DNA methyltransferase induction after SAHA/GemBuMel (BGMS) with the addition of azacitidine (DAC).

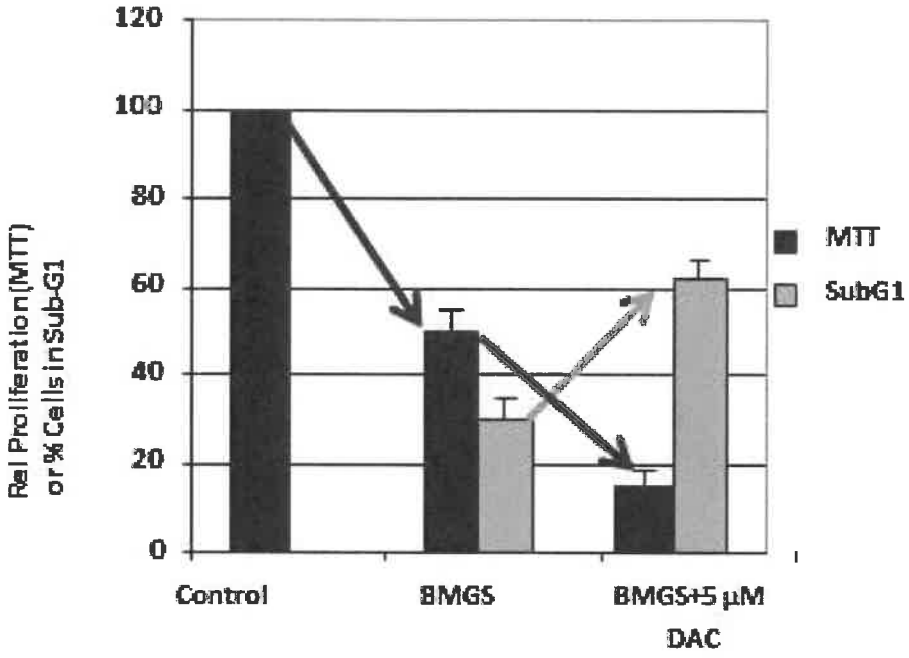

Fig. 4-B. Effect on cytotoxicity and apoptosis of the addition of azacitidine (DAC) to SAHA/GemBuMel (BGMS).

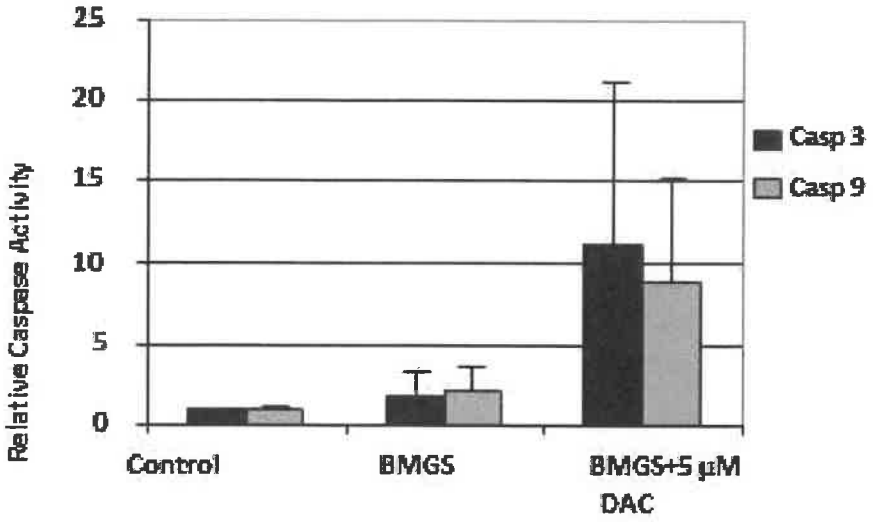

Fig. 4-C. Increase of caspase activity of the addition of azacitidine (DAC) to SAHA/GemBuMel (BGMS).

These results are in keeping with observations from other investigators, who have shown high level of synergy in DLCL cell lines resulting from concurrent exposure to HDAC inhibitors and DNA methyltransferase inhibitors.[12]

5-Azacitidine is a pyrimidine nucleoside analog of cytidine. High doses are cytotoxic while hypomethylation occurs at lower doses. The concentration of 5-azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis, and non-proliferating cells are relatively insensitive to the drug. The recommended hypomethylating dose is 75 mg/m^2 daily for seven days, every four weeks. This dose is associated with significant myelosuppression but minimal nonhematological toxicity.
The combination of azacitidine at (75 mg/m2 daily x 5-7 days) with vorinostat is known to be safe and tolerable in repetitive cycles, with minimal non-hematologic toxicity.[13, 14] Similar to SAHA, clinical combinations of azacitidine with standard-dose chemotherapy are feasible allowing administration of chemotherapy at full doses.[15]

In conclusion, the preclinical results by Valdez and Andersson provide the rationale for the clinical testing of azacitidine combined with SAHA and high-dose GemBuMel in refractory lymphomas. We hypothesize that the combined SAHA/azacitidine epigenetic platform will safely increase the antitumor activity of GemBuMel in this challenging patient population.

3.0 Patient Eligibility

3.1 Inclusion:

3.1.1. Age 15 to 65 years.
3.1.2. Patients with Hodgkin's lymphoma with one or more of the following:
  a) Less than complete response to first-line chemotherapy.
  b) Relapse within 12 months of completion of first-line chemotherapy
  c) Relapse within a prior irradiation field.

d) Less than complete metabolic response to second-line chemotherapy
e) Second relapse or beyond.
f) Extranodal disease at the time of relapse.
g) Presence of B symptoms at the time of persistent disease upon completion of first-line chemotherapy, relapse or progressive disease.
h) Bulky disease (defined as any lesion greater than 5 cm) at the time of persistent disease upon completion of first-line chemotherapy, relapse or progressive disease.

3.1.3. Patients with non-Hodgkin's lymphoma and one or more of the following:
3.1.3.1. Diffuse large B-cell lymphoma with one or more of the following:
a) Primary refractory disease.
b) Relapse within 12 months of completion of first-line therapy.
c) Secondary IPI >1.
d) Less than PR to first-line salvage chemotherapy.
e) Kinetic failure after salvage chemotherapy.
f) Prior treatment with 3 or more lines of therapy.
g) Patients with double-hit or triple-hit NHL, in any state of the disease.
3.1.3.2. Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) in any stage of the disease.
3.1.3.3. Angioimmunoblastic T-cell lymphoma (AITL) in any stage of the disease.
3.1.3.4. Refractory or recurrent Burkitt's lymphoma.
3.1.3.5. Any other lymphoma that is refractory or relapsed and that does not qualify for treatment protocols of higher priority.

3.1.4. Adequate renal function, as defined by estimated serum creatinine clearance >/=50 ml/min (MDRD method from National Kidney Disease Education Program, NKDEP) and/or serum creatinine </= 1.8 mg/dL.
3.1.5. Adequate hepatic function, as defined by SGOT and/or SGPT </= 3 x upper limit of normal; serum bilirubin and alkaline phosphatase </= 2 x upper limit of normal.
3.1.6. Adequate pulmonary function with FEV1, FVC and DLCO >/= 50% of expected corrected for hemoglobin.
3.1.7. Adequate cardiac function with left ventricular ejection fraction >/= 40%. No uncontrolled arrhythmias or symptomatic cardiac disease.
3.1.8. Zubrod performance status <2.
3.1.9. Negative Beta HCG text in a woman with child-bearing potential, defined as not post-menopausal for 12 months or no previous surgical sterilization.

3.2 Exclusion:

3.2.1. Patients with grade >/= 3 non-hematologic toxicity from previous therapy that has not resolved to </= grade 1.
3.2.2. Patients with prior whole brain irradiation.
3.2.3. Patients with active hepatitis B, either active carrier (HBsAg +) or viremic (HBV DNA >/=10,000 copies/mL, or >/= 2,000 IU/mL).
3.2.4. Evidence of either cirrhosis or stage 3-4 liver fibrosis in patients with chronic hepatitis C or positive hepatitis C serology.
3.2.5. Patients with active inflammatory bowel disease.
3.2.6. Active infection requiring parenteral antibiotics.
3.2.7. HIV infection, unless the patient is receiving effective antiretroviral therapy with undetectable viral load and normal CD4 counts.
3.2.8. Patients having received radiation therapy in the month prior to enrollment.

4.0 Pretreatment evaluation

4.1. Studies listed below will be done within 30 days prior to start treatment only if these were not done before study entry either as part of diagnostic or routine pre-transplant workup.

Lab work:
Serum HCG in all female patients of childbearing potential, CBC with differential, SGPT, SGOT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, PT and PTT, complete urinalysis, blood typing and infectious disease panel.
Chest X ray.
Pulmonary function tests with DLCO.
EKG.
Echocardiogram or MUGA.
CT scans of neck, chest, abdomen and pelvis.

4.2. The following will be performed before admission if clinically indicated:
Brain MRI.
Bone marrow biopsy and aspirate with cytogenetic studies

4.3 Pharmacodynamic study

This correlative study will be optional for patients participating in this trial. We will determine whether azacitidine at the doses given in this study effectively inhibit DNMT3A and DNMT3B in mononuclear cells extracted from 20-cc of blood drawn at the following timepoints:

1. For baseline any time after the informed consent document is signed but before first dose of azacitidine is given.
2. With am labs on Days -9, -5, and -1.

The correlative study analyses will be conducted in the laboratory of Drs. Valdez and Andersson.

5.0 Study Registration

Each patient will be evaluated and approved for enrollment by the primary attending physician and the Study Chairman (or his designee). The study research coordinator will register each patient on protocol. All protocol participants will be registered in the institutional CORe system.

6.0 Treatment Plan

Treatment will not commence until resolution of prior toxicities to grade 1 or less.

Acetaminophen (Tylenol) shall not be administered for 72 hr before and on the day of administration of Busulfan or Melphalan. Voriconazole, posaconazole, fluconazole, itraconazole and metronidazole will be avoided from 7 days before start of chemotherapy to Day -1.

Table 2.a. Azacitidine-SAHA-GemBuMel schedule (Inpatient Busulfan Test Dose)

Day	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2
Palifermin																	

per standard of care	X	X	X												X	X	X
Admission			X														
Busulfan test dose (if inpatient)				X													
Vorinostat 1,000 mg PO daily				X	X	X	X	X	X	X	X	X	X				
Azacitidine (dose per level)				X	X	X	X	X	X	X	X	X	X				
Gemcitabine 75 mg/m2 followed by CI at 10 mg/m2/min							X					X					
Busulfan							X	X	X	X							
Melphalan												X	X				
PBPC infusion															X		

Table 2.b. Azacitidine-SAHA-GemBuMel schedule (Outpatient Busulfan Test Dose)

Day	**-14**	**-13**	**-12**	**-11**	**-10**	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**
Palifermin per standard of care	X	X	X												X	X	X
Admission			X														
Vorinostat 1,000 mg PO daily				X	X	X	X	X	X	X	X	X	X				
Azacitidine (dose per level)				X	X	X	X	X	X	X	X	X	X				
Gemcitabine 75 mg/m2 followed by CI at 10 mg/m2/min							X					X					
Busulfan							X	X	X	X							
Melphalan												X	X				
PBPC infusion															X		

Chemotherapy agents' doses and administration.
Chemotherapy agents used in the proposed treatment plans will be dosed and administered as outlined below.

Vorinostat will be administered within 1 hour before the dose of azacitidine. Repeat a full dose if emesis occurs within 30 minutes and tablets/tablet fragments are found in the vomit. If given inpatient, nurse should stay and witness the patient taking the drug.

Azacitidine with be administered intravenously (dose per cohort), starting on Day -11. It will be followed immediately by gemcitabine on days -8 and -3, by busulfan on Days -7, -6 and -5, and by melphalan on Days -3 and -2.

Gemcitabine will be administered as a loading dose of 75 mg/m2 followed by continuous infusion. It will be followed immediately by busulfan on Day -8 and melphalan on Day -3.

Busulfan pharmacokinetic-guided treatment (PK-guided). The Busulfan test dose can be

administered either as an outpatient before Day -12 or as an inpatient on Day -11. The "test dose" of 32 mg/m^2 will be based on actual body weight to be administrated over 60 minutes. Busulfan pharmacokinetics will be performed with the test dose and the first dose on day-8. The doses of days -6 and -5 will be subsequently adjusted to target an AUC of 4,000 microMol.min^{-1}.

In the event that PK adjusting were not possible a dose of busulfan of 100 mg/m2 will be administered on Days -6 and -5.

Melphalan will be administered at 60 mg/m2 on Days -3 and -2.

Patients with CD20+ tumors will receive rituximab 375 mg/m2 on Day -9.

6.2. Supportive Treatment

Patients will receive standard supportive treatment as outlined below.

1. Dexamethasone 8 mg IV BID from day -11 AM to day -2 PM. Omit any other dexamethasone for chemotherapy premedication.
2. G-CSF per departmental standard of care.
3. Mucositis supportive care:
   - 3.1. Palifermin per departmental standard of care with 3 doses to be administered prior to start chemo on days -14, -13 and -12, and 3 doses after the last chemo starting on day 0. Doses can be capped at vial size.
   - 3.2. Caphosol oral rinses 30 mL four times a day will be used from day -9.
   - 3.3. Oral glutamine, 15 g four times a day, swished, gargled and swallowed will be started on day -9.
4. Pyridoxine 100 mg IV/PO TID from day -1.

Other supportive treatment such as antiemetics or infection prophylaxis, as per departmental standard of care.

Dose Escalation

Dose escalation will proceed as shown on Table 3 (levels 1a-7a). If level 1a is too toxic, the dose of gemcitabine will be de-escalated to 2,475 and azacitidine will be escalated as shown (levels 1b-7b).

Table 3. Dose Escalation

Level	Azacitidine (mg/ m2/day)	Vorinostat (mg/day)	Gemcitabine (mg/m2/day)	Busulfan (mg/m2/d or AUC/day)	Melphalan (mg/m2/d)
1a	15	1000	2775	100 or 4,000	60
2a	25	1000	2775	100 or 4,000	60
3a	35	1000	2775	100 or 4,000	60
4a	45	1000	2775	100 or 4,000	60
5a	55	1000	2775	100 or 4,000	60
6a	65	1000	2775	100 or 4,000	60
7a	75	1000	2775	100 or 4,000	60
1b	15	1000	2475	100 or 4,000	60
2b	25	1000	2475	100 or 4,000	60
3b	35	1000	2475	100 or 4,000	60
4b	45	1000	2475	100 or 4,000	60
5b	55	1000	2475	100 or 4,000	60
6b	65	1000	2475	100 or 4,000	60
7b	75	1000	2475	100 or 4,000	60

6.3 Recommendations for Post-Transplant Radiotherapy

Involved field radiotherapy, starting 4-6 weeks after transplant, should be considered for patients who have engrafted neutrophils and platelets and who presented bulky (>5 cm) PET+ lesions at HDC (strongly recommended) or have persistent PET+ lesions at day +30 post-SCT (strongly recommended). It should also be considered for PET+ lesions measuring <5 cm at HDC, particularly if previously bulky at the time of relapse or progression. In all cases feasibility of radiotherapy will be assessed based on prior radiation exposure and possibility to treat all relevant sites of disease.

7.0 Post-Treatment Evaluation

During the treatment administration and until day +100 all patients will be monitored for toxicity; these will be evaluated according to CTCAE v4.0. While admitted in hospital, patients will be monitored on a regular basis. Once discharged patient will come once a week or as determined by the primary physician until day +30. Treatment completion assessment will be performed around day +100.

Antitumor responses will be evaluated according to the CIBMTR guidelines.

7.1. Treatment completion assessment. To be performed around day +100.

History, physical exam
Lab work: CBC, differential, platelets, SGPT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, complete urinalysis.

Tumor response: CT of the chest, abdomen and pelvis, as medically indicated. Bone marrow aspiration and biopsy if medically indicated.

7.2. Off-Study Criteria: study duration will be the time from study registration until death, patient request, or day +100 after transplantation, whichever occurs first.

8.0 Determination of Body Surface Area

For patients whose actual body weight is $\leq$ 20% above ideal body weight (defined by the MD Anderson dosing calculator), the actual body weight is used to calculate the body surface area (BSA). The actual body weight will also be used to calculate the BSA for the busulfan test dose and rituximab (CD20+ tumors). For purposes of gemcitabine and melphalan dosing, patients whose actual body weight is >20% above ideal body weight, an "adjusted body weight" is calculated using the midpoint between the actual and ideal body weight, and defining that as the adjusted body weight. That adjusted body weight is then used to calculate an "adjusted body surface area" that is used for chemotherapy dosing calculation purposes.

9.0 Determination of Dose-Limiting Toxicity (DLT)

9.1. Starting Dose and Dose Escalation

Patients will be enrolled as described in the statistical section. No more than 2 patients will be enrolled at any one time in a new dose level. Until the toxicities of at least 1 of those 2 patients are assessed and determined not to be DLT, no more patients will be enrolled at the new dose level. If, based on medical considerations, a third patient has to initiate treatment before that time, this third patient will be enrolled at the prior dose level.

9.2. Definition of DLT

Dose limiting toxicity will be defined as any grade 4 or 5 non-hematological, non-infectious toxicity attributable to Azacitidine/Vorinostat/GemBuMel as well as grade 3 mucositis and grade 3 skin toxicity lasting for more than 3 days at their peak severity (i.e., grade 3). Consideration of DLT will exclude asymptomatic and self-limited elevation of the transaminases as well as laboratory serum metabolic values not reflecting end-organ function.

Enrollment will continue to proceed following the adaptive design as determined by the continuous reassessment method (CRM). CRM will assign a dose level (e.g., dose X) to up to 2 new patients (e.g., patient A and B). If, based on medical considerations, subsequent patients (e.g., patients C, D...) have to initiate treatment before the toxicities of patients A or B have been assessed, these subsequent patients will be treated at the same level, i.e., dose X. Until the toxicities of at least one of patients A and B are assessed and determined not to be DLT, no patients will be enrolled at dose levels other than level X.

10.0 Reporting Requirements

Patients will be followed up to day +100 after transplant or until documentation of reversal of toxicities related to this treatment. The intensity of adverse events (AE) will be assessed according to the Common Terminology Criteria v4.0 (CTCAE). Adverse events and protocol deviations will be reported accordingly to MDACC policy and procedures. Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

10.1. Adverse events (toxicities) known to be produced by the chemotherapy regimen:
Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis
Hepatic: self-limited elevations of liver function enzymes; venoocclusive disease
Pulmonary: acute dyspnea, pulmonary fibrosis and interstitial pneumonitis.
Skin: rash.

10.2. Adverse events (toxicities) known to be produced by other treatment components:
The following events are not considered to be significant in relationship with the study treatment, would not be considered adverse events, and will not be collected in the study database.
Myelosuppression-related: neutropenia, anemia thrombocytopenia, platelets and RBCs transfusions.
Flu-like symptoms: low grade fever, headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia.
Mood alteration: depression, anxiety, and agitation
Readmissions (lasting <10 days)
Low blood pressure due to dehydration requiring fluid replacement
Fluid overload.
Fatigue.
Laboratory serum metabolic values not reflecting end-organ (hepatic, renal) function and or those considered associated to the original disease
Events that are identified to be related to the supportive treatment, e.g., steroids, palifermin, antibiotics.

10.3. Adverse Events Considered Serious (SAEs):
1. Graft failure/rejection
2. Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation)
3. Readmissions from any cause resulting in a prolonged hospitalization (>10 days).
4. Any expected or unexpected event resulting in an irreversible condition and/ or leading to death.

SAEs will be reported to the PI or his designate, who in turn will notify the IRB following institutional policy.

11.0 Statistical Considerations

Dose-Finding Design. This is a phase I dose-finding study to determine an optimal dose combination of (Azacitidine, Gemcitabine) = (Aza, Gem) when given together and in combination with SAHA, IV Busulfan, and Melphalan as a preparative regimen for autologous stem cell transplant (SCT) for patients with refractory lymphoma. Pre-SCT at day 0, Gemcitabine will be given on days -8 and -3, IV Busulfan will be given on days -8, -7, -6, -5, Melphalan will be given on days -3, -2, and both SAHA and Aza will be given on days -8, -7, -6, -5, -4, -3, -2 Seven dose levels will be defined in terms of the doses and schedules of (Aza, Gem). The primary outcome is time to toxicity, where toxicity defined as (i) any grade 4 or 5 non-hematologic toxicity, excluding infection or (ii) grade 3 or higher mucositis or skin rash that lasts 3 days or longer. Both events are defined within a time window of 28 days following SCT. The primary goal will be to determine the "optimal" dose level, defined as a dose level having toxicity probability closest to the target 0.20. The time-to-event continual reassessment method (TiTE-CRM) will be used to find the optimal dose (Cheung and Chappell, 2000).[16] The assumed toxicity probability skeleton for the underlying model will be c(.02, .05, .08, .12, 0.16, .20, 0.24). A maximum of 60 patients will be treated in cohorts of size 2, starting at dose level 1, and not skipping an untried dose level when escalating. An accrual rate of 2 patients per month will be assumed. Since the TiTE CRM does not include a rule to stop the trial early if the lowest dose level is too toxic, we include the following additional safety monitoring rule, which will be applied to patients treated at dose level 1. The trial will be stopped early if the lowest dose level is too toxic. Dose escalation will proceed as shown on Table 11.1, starting with levels 1a-7a. If level 1a is too toxic per the Additional Safety Monitoring Rule For The First Dose, given below, the dose of gemcitabine will be de-escalated to 2,475 and azacitidine will be escalated as shown, and the TiTE-CRM design will be re-started using levels 1b-7b.

Operating Characteristics. The operating characteristics of this design, given in Table 11.2, were computed using the program dfcrm, provided by K. Cheung and freely available at the CRAN R source website.

Table 11.1 Dose levels of Azacitidine and Gemcitabine combinations.

Level	Azacitidine (mg/ m2/day)	Vorinostat (mg/day)	Gemcitabine (mg/m2/day)	Busulfan (mg/m2/d or AUC/day)	Melphalan (mg/m2/d)
1a	15	1,000	2,775	100 or 4,000	60
2a	25	1,000	2,775	100 or 4,000	60
3a	35	1,000	2,775	100 or 4,000	60
4a	45	1,000	2,775	100 or 4,000	60
5a	55	1,000	2,775	100 or 4,000	60
6a	65	1,000	2,775	100 or 4,000	60
7a	75	1,000	2,775	100 or 4,000	60
1b	15	1,000	2,475	100 or 4,000	60
2b	25	1,000	2,475	100 or 4,000	60
3b	35	1,000	2,475	100 or 4,000	60
4b	45	1,000	2,475	100 or 4,000	60
5b	55	1,000	2,475	100 or 4,000	60
6b	65	1,000	2,475	100 or 4,000	60
7b	75	1,000	2,475	100 or 4,000	60

Table 11.2. Operating Characteristics of the TiTE-CRM Design

		Dose Levels (See table 11.1)						
		1	**2**	**3**	**4**	**5**	**6**	**7**
Scenario								
1	True Prob(Tox)	0.10	**0.02**	0.30	0.40	0.50	0.60	0.70
	% Selected	17.8	**62.6**	19.0	0.0	0.0	0.0	0.0
	Average N Patients Treated	15.9	**26.9**	12	3.2	1.1	0.5	0.4
	Average N Patients w/Tox	1.6	**5.3**	3.6	1.3	0.6	0.3	0.2
2	True Prob(Tox)	**0.30**	0.40	0.50	0.60	0.70	0.80	0.90

	% Selected	**99.4**	0.6	0.0	0.0	0.0	0.0	0.0
	Average N Patients Treated	**53.9**	3.7	1.3	0.6	0.3	0.1	0.1
	Average N Patients w/Tox	**16.1**	1.4	0.7	0.4	0.2	0.1	0.1
3	True Prob(Tox)	0.05	0.10	**0.20**	0.40	0.60	0.80	0.90
	% Selected	0.20	24.4	**66.6**	8.8	0.0	0.0	0.0
	Average N Patients Treated	5.3	18.0	**26.7**	7.8	1.5	0.5	0.3
	Average N Patients w/Tox	0.3	1.8	**5.3**	3.1	0.9	0.4	0.3
4	True Prob(Tox)	0.05	0.1	0.15	**0.20**	0.25	0.3	0.35
	% Selected	0.0	5.3	24.1	**38.4**	22.8	7.0	2.5
	Average N Patients Treated	3.0	6.4	12.4	**16.0**	11.0	5.7	5.5
	Average N Patients w/Tox	0.2	0.6	1.9	**3.2**	2.7	1.7	1.9
5	True Prob(Tox)	0.02	0.06	0.1	0.14	**0.20**	0.26	0.32
	% Selected	0	0.2	4.9	25.1	**40.6**	21.6	7.6
	Average N Patients Treated	1.7	2.6	6.0	12.9	**15.7**	11.0	10.1
	Average N Patients w/Tox	0.1	0.2	0.6	1.8	**3.1**	2.8	3.2

6	True Prob(Tox)	0.02	0.05	0.08	0.11	**0.20**	0.32	0.40
	% Selected	0.0	0.0	2.2	24.4	**54.0**	17.9	1.4
	Average N Patients Treated	1.5	2.3	5	14.5	**20.3**	10.4	5.9
	Average N Patients w/Tox	0.0	0.1	0.40	1.6	**4.0**	3.3	2.3
7	True Prob(Tox)	0.05	**0.15**	**0.25**	0.40	0.50	0.60	0.70
	% Selected	1.8	**50.2**	**44.3**	3.6	0.0	0.0	0.0
	Average N Patients Treated	7.0	**24.8**	**20.4**	5.4	1.4	0.6	0.5
	Average N Patients w/Tox	0.4	**3.7**	**5.1**	2.1	0.7	0.4	0.3
8	True Prob(Tox)	0.01	0.02	0.05	0.08	0.11	0.14	**0.17**
	% Selected	0.0	0.0	0.0	0.40	4.6	12.8	**82.3**
	Average N Patients Treated	1.2	1.3	1.8	3.0	5.2	8.1	**39.4**
	Average N Patients w/Tox	0.0	0.0	0.1	0.2	0.6	1.1	**6.7**

Additional Safety Monitoring Rule For The First Dose

Since the TiTE CRM does not include a rule to stop the trial early if the lowest dose level is too toxic, we include the following additional safety monitoring rule, which will be applied to patients treated at dose level 1. The trial will be stopped early if the lowest dose level is too toxic. Formally, assuming that q = Prob(toxicity at dose level 1) follows a beta(0.20, 0.80) prior, the

trial will be stopped if Pr(q > 0.2 | Data) > 0.95. This probability inequality will be applied starting at patient #6 at dose level 1, and it implies that the trial will be stopped if

[# DLTs observed at dose level 1] / [# Patients treated at dose 1] is greater than or equal to 3/5, 4/7, 5/9, 6/13, 7/17, 8/19, 9/23, 10/27, 11/31, 12/35, 13/39, 14/43, 15/47, 16/51, 17/55, 18/59.

Note that, for example, if 3 toxicities are seen in either the first 3 or 4 patients at dose level 1, then the trial will be stopped.

Table 11.3. Operating characteristics of the Dose Level 1 safety stopping rule.

		Sample Size Quartiles		
True Toxicity Rate	**Probability of Stopping Early**	**25**	**50 (median)**	**75**
10%	0.01	60	60	60
20%	0.18	60	60	60
30%	0.72	11	20	60
40%	0.98	5	11	23

Secondary Outcomes. Complete remission (CR), defined as resolution of all lesions by day 100 post SCT, and relapse-free survival (RFS) time.

Data Analysis. The data will be analyzed by fitting time-to-toxicity models to the final data, and summarizing the posterior distributions of the probability of overall toxicity and of each adverse event in the definition of toxicity at the MTD and at the other doses, by tabulating the counts and rates of all secondary events, including CR, both overall and cross-tabulated with dose, and fitting appropriate logistic or other n=binary outcome regression models[17] to assess possible patterns of change with dose. RFS time will be estimated by the method of Kaplan and Meier.[18]

Trial Conduct. The trial will be conducted using the TiTE CRM subroutine of the dfcrm program, with W. Wei of the Department of Biostatistics maintaining the data set of doses and follow-up times provided by a designated Research Nurse or Study Coordinator in the Department of Stem Cell Transplantation and Cellular Therapy.

12.0 Background Drug Information

12.1. AZACITIDINE

U.S. Brand Names: Vidaza™
Index Terms: 5-Azacytidine; 5-AZC; AZA-CR; Azacytidine; Ladakamycin
Use: Treatment of myelodysplastic syndrome (MDS)
Warnings
Concerns related to adverse effects:

• Bone marrow suppression: Neutropenia, thrombocytopenia, and anemia are common; may cause therapy delays and/or dosage reductions.

• Hepatotoxicity: May be hepatotoxic, progressive hepatic coma leading to death has been reported (rare) in patients with extensive tumor burden, especially those with a baseline albumin <30 g/L.

• Renal toxicities: Serum creatinine elevations, renal tubular acidosis, and renal failure have been reported with combination chemotherapy; decrease or withhold dose for unexplained elevations in BUN or serum creatinine, or reductions in serum bicarbonate to <20 mEq/L.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment. Patients with hepatic impairment were excluded from clinical studies. Use is contraindicated in patients with advanced malignant hepatic tumors.

• Renal impairment: Use with caution in patients with renal impairment; dose adjustment may be required. Patients with renal impairment were excluded from clinical studies.

Special populations:

• Pediatrics: Not FDA approved for use in children.

Special handling:

• Hazardous agent: Use appropriate precautions for handling and disposal

Contraindications
Hypersensitivity to azacitidine, mannitol, or any component of the formulation; advanced malignant hepatic tumors

Adverse Reactions
>10%:

Cardiovascular: Peripheral edema (7% to 19%), chest pain (16%), pallor (16%), pitting edema (15%)

Central nervous system: Fever (30% to 52%), fatigue (13% to 36%), headache (22%), dizziness (19%), anxiety (5% to 13%), depression (12%), insomnia (9% to 11%), malaise (11%), pain (11%)

Dermatologic: Bruising (19% to 31%), petechiae (11% to 24%), erythema (7% to 17%), skin lesion (15%), rash (10% to 14%), pruritus (12%)

Endocrine & metabolic: Hypokalemia (6% to 13%)

Gastrointestinal: Nausea (48% to 71%), vomiting (27% to 54%), diarrhea (36%), constipation (34% to 50%), anorexia (13% to 21%), weight loss (16%), abdominal pain (11% to 16%), abdominal tenderness (12%)

Hematologic: Thrombocytopenia (66% to 70%; grades 3/4: 58%), anemia (51% to 70%; grades 3/4: 14%), neutropenia (32% to 66%; grades 3/4: 61%), leukopenia (18% to 48%; grades 3/4: 15%), febrile neutropenia (14% to 16%; grades 3/4: 13%), myelosuppression (nadir: days 10-17; recovery: days 28-31)

Local: Injection site reactions (14% to 29%): Erythema (35% to 43%; more common with I.V. administration), pain (19% to 23%; more common with I.V. administration), bruising (5% to 14%)

Neuromuscular & skeletal: Weakness (29%), rigors (26%), arthralgia (22%), limb pain (20%), back pain (19%), myalgia (16%)

Respiratory: Cough (11% to 30%), dyspnea (5% to 29%), pharyngitis (20%), epistaxis (16%), nasopharyngitis (15%), upper respiratory tract infection (9% to 13%), pneumonia (11%), crackles (11%)

Miscellaneous: Diaphoresis (11%)

5% to 10%:

Cardiovascular: Cardiac murmur (10%), hypertension (≤9%), tachycardia (9%), hypotension (7%), syncope (6%), chest wall pain (5%)

Central nervous system: Lethargy (7% to 8%), hypoesthesia (5%), post-procedural pain (5%)

Dermatologic: Cellulitis (8%), urticaria (6%), dry skin (5%), skin nodule (5%)

Gastrointestinal: Gingival bleeding (10%), oral mucosal petechiae (8%), stomatitis (8%), weight loss (≤8%), dyspepsia (6% to 7%), hemorrhoids (7%), abdominal distension (6%), loose stools (6%), dysphagia (5%), oral hemorrhage (5%), tongue ulceration (5%)

Genitourinary: Dysuria (8%), urinary tract infection (8% to 9%)

Hematologic: Hematoma (9%), post-procedural hemorrhage (6%)

Local: Injection site reactions: Pruritus (7%), hematoma (6%), rash (6%), granuloma (5%), induration (5%), pigmentation change (5%), swelling (5%)

Neuromuscular & skeletal: Muscle cramps (6%)

Renal: Hematuria (≤6%)

Respiratory: Rhinorrhea (10%), rales (9%), wheezing (9%), breath sounds decreased (8%), pharyngolaryngeal pain (6%), pleural effusion (6%), postnasal drip (6%), rhinitis (6%), rhonchi (6%), nasal congestion (6%), atelectasis (5%), sinusitis (5%)

Miscellaneous: Lymphadenopathy (10%), herpes simplex (9%), night sweats (9%), transfusion reaction (7%), mouth hemorrhage (5%)

<5%, postmarketing, and/or case reports: Abscess (limb, perirectal), acute febrile neutrophilic dermatosis (Sweet's syndrome), agranulocytosis, anaphylactic shock, atrial fibrillation, azotemia, blastomycosis, bone marrow depression/failure, bone pain aggravated, cardiac failure, cardiorespiratory arrest, catheter site hemorrhage, cellulitis, cerebral hemorrhage, CHF, cholecystectomy, cholecystitis, congestive cardiomyopathy, dehydration, diverticulitis, eye hemorrhage, fibrosis (interstitial and alveolar), gastrointestinal hemorrhage, glycosuria, hemoptysis, hepatic coma, hypersensitivity reaction, hypophosphatemia, infection (bacterial), injection site infection, injection site necrosis, interstitial lung disease, intracranial hemorrhage, leukemia cutis, lung infiltration, melena, neutropenic sepsis, orthostatic hypotension, pancytopenia, pneumonitis, polyuria, pyoderma gangrenosum, renal failure, renal tubular acidosis, seizure, respiratory distress, sepsis, septic shock, serum bicarbonate levels decreased, serum creatinine increased, splenomegaly, systemic inflammatory response syndrome, toxoplasmosis, tumor lysis syndrome

Metabolism/Transport Effects
None known.

Drug Interactions Open Interactions
BCG: Immunosuppressants may diminish the therapeutic effect of BCG. *Risk X: Avoid combination*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine.

Specifically, the risk for agranulocytosis may be increased. *Risk X: Avoid combination*

Coccidioidin Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioidin Skin Test. *Risk C: Monitor therapy*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or other non-disease modifying antirheumatic drugs (non-DMARDs) is permitted, and this warning seems to particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Mechanism of Action
Antineoplastic effects may be a result of azacitidine's ability to promote hypomethylation of DNA leading to direct toxicity of abnormal hematopoietic cells in the bone marrow.

Pharmacodynamics/Kinetics
Absorption: SubQ: Rapid and complete

Distribution: V_d: I.V.: 76 ± 26 L; does not cross blood-brain barrier

Metabolism: Hepatic; hydrolysis to several metabolites

Bioavailability: SubQ: ~89%

Half-life elimination: I.V., SubQ: ~4 hours

Time to peak, plasma: SubQ: 30 minutes

Excretion: Urine (50% to 85%); feces (minor)

Dosage
Children: I.V.: Refractory AML (unlabeled use): 250 mg/m2/dose days 4 and 5 every 4 weeks (Steuber, 1996) **or** 300 mg/m2/dose days 4 and 5 every 4 weeks (Hurwitz, 1995)

Adults:

MDS: I.V., SubQ: 75 mg/m2/day for 7 days repeated every 4 weeks. Dose may be increased to 100 mg/m2/day if no benefit is observed after 2 cycles and no toxicity other than nausea and vomiting have occurred. Treatment is recommended for at least 4 cycles; treatment may be continued as long as patient continues to benefit.

Note: Alternate (unlabeled) schedules (which have produced hematologic response) have been used for convenience in community oncology centers (Lyons, 2009):

75 mg/m2/day for 5 days (Mon-Fri), 2 days rest (Sat, Sun), then 75 mg/m2/day for 2 days (Mon, Tues); repeat cycle every 28 days **or**

50 mg/m2/day for 5 days (Mon-Fri), 2 days rest (Sat, Sun), then 50 mg/m2/day for 5 days (Mon-Fri); repeat cycle every 28 days **or**

75 mg/m2/day for 5 days (Mon-Fri), repeat cycle every 28 days

AML (unlabeled use): SubQ: 75 mg/m2/day for 7 days repeated every 4 weeks (Sudan, 2006)

Elderly: Refer to adult dosing; due to the potential for decreased renal function in the elderly, select dose carefully and closely monitor renal function

Monitoring Parameters
Liver function tests, electrolytes, CBC with differential and platelets, renal function tests (BUN and serum creatinine) should be obtained prior to initiation of therapy. Electrolytes, renal function (BUN and creatinine), CBC should be monitored prior to each cycle and periodically as needed to monitor response and toxicity.

Administration
SubQ: Premedication for nausea and vomiting is recommended. The manufacturer recommends equally dividing volumes >4 mL into 2 syringes and injecting into 2 separate sites; however, policies for maximum SubQ administration volume may vary by institution; interpatient variations may also apply. Administer subsequent injections at least 1 inch from previous injection sites. Allow refrigerated suspensions to come to room temperature (up to 30 minutes) prior to administration. Resuspend by inverting the syringe 2-3 times and then rolling the syringe between the palms for 30 seconds. If azacitidine suspension comes in contact with the skin, immediately wash with soap and water.

I.V.: Premedication for nausea and vomiting is recommended. Infuse over 10-40 minutes; infusion must be completed within 1 hour of (vial) reconstitution.

Hazardous agent; use appropriate precautions for handling and disposal

Dosage Forms

Injection, powder for suspension: 100 mg [contains mannitol 100 mg]

12.2. Vorinostat (SAHA)

Therapeutic Category: Antineoplastic Agent, Histone Deacetylase Inhibitor
Adverse reactions:

>10%:

Cardiovascular: Peripheral edema (13%)

Central nervous system: Fatigue (52%), chills (16%), dizziness (15%), headache (12%), fever (11%)

Dermatologic: Alopecia (19%), pruritus (12%)

Endocrine & metabolic: Hyperglycemia (8% to 69%; grade 3: 5%), dehydration (1% to 16%)

Gastrointestinal: Diarrhea (52%), nausea (41%), taste alteration (28%), anorexia (24%), weight loss (21%), xerostomia (16%), constipation (15%), vomiting (15%), appetite decreased (14%)

Hematologic: Thrombocytopenia (26%; grades 3/4: 6%), anemia (14%; grades 3/4: 2%)

Neuromuscular & skeletal: Muscle spasm (20%)

Renal: Proteinuria (51%), creatinine increased (16% to 47%)

Respiratory: Cough (11%), upper respiratory infection (11%)

1% to 10%:

Cardiovascular: QTc prolongation (3% to 4%)

Dermatologic: Squamous cell carcinoma (4%)

Respiratory: Pulmonary embolism (5%)

≤1% (postmarketing, and/or case reports): Abdominal pain, angioneurotic edema, blurred vision, chest pain, cholecystitis, deafness, diverticulitis, dysphagia, DVT, enterococcal infection, exfoliative dermatitis, gastrointestinal bleeding, gastrointestinal hemorrhage, Guillain-Barré syndrome, hemoptysis, hypertension, hypokalemia, hyponatremia, infection, lethargy, leukopenia, MI, neutropenia, pneumonia, renal failure, sepsis, spinal cord injury, streptococcal bacteremia, stroke (ischemic), syncope, T-cell lymphoma, tumor hemorrhage, ureteric obstruction, ureteropelvic junction obstruction, urinary retention, vasculitis, weakness

Drug Interactions
Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Artemether: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Chloroquine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Ciprofloxacin (Systemic): May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Divalproex: May enhance the thrombocytopenic effect of Vorinostat. This may increase the risk

of gastrointestinal bleeding. Risk C: Monitor therapy
Dronedarone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Dronedarone. Risk X: Avoid combination
Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk D: Consider therapy modification
Lumefantrine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Pimozide: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Pimozide. Risk X: Avoid combination
QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. Risk D: Consider therapy modification
QuiNINE: QTc-Prolonging Agents may enhance the QTc-prolonging effect of QuiNINE. QuiNINE may enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. Risk X: Avoid combination
Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. Risk X: Avoid combination
Toremifene: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Toremifene. The risk for potentially dangerous arrhythmias may be increased. Risk X: Avoid combination
Valproic Acid: May enhance the thrombocytopenic effect of Vorinostat. This may increase the risk of gastrointestinal bleeding. Risk C: Monitor therapy
Vandetanib: QTc-Prolonging Agents may enhance the arrhythmogenic effect of Vandetanib. Risk X: Avoid combination
Vitamin K Antagonists (e.g., warfarin): Vorinostat may enhance the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy
Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. Risk X: Avoid combination

Mechanism of Action

Inhibition of histone deacetylase enzymes, HDAC1, HDAC2, HDAC3, and HDAC6, which catalyze acetyl group removal from protein lysine residues (including histones and transcription factors). Inhibition of histone deacetylase results in accumulation of acetyl groups, leading to alterations in chromatin structure and transcription factor activation causing termination of cell growth leading to cell death.

Pharmacodynamics/Kinetics

There is not much difference in the extent and rate of absorption of vorinostat between fasted and fed state. The peak serum concentration is achieved at 2-4 hours with an estimated bioavailability of around 45%. It binds to plasma proteins by approximately 70%. Its major pathways of metabolism involve glucuronidation, mainly by the hepatic UGT2B17 and extrahepatic UGT1A8 enzymes,[19] and hydrolysis followed by β-oxidation to inactive metabolites. There is negligible biotransformation by cytochromes P450. Less than 1% of the dose is recovered as unchanged drug in urine. The mean terminal half-life was around 2 hours for both vorinostat and the *O*-glucuronide metabolite.
Protein binding: ~71%
Metabolism: Glucuronidated and hydrolyzed (followed by beta-oxidation) to inactive metabolites
Bioavailability: Fasting: ~43%
Half-life elimination: ~2 hours

Time to peak, plasma: With high-fat meal: ~4 hours (range: 2-10 hours)
Excretion: Urine: 52% (<1% as unchanged drug, ~52% as inactive metabolites)

Dosage

Oral: Adults: Cutaneous T-cell lymphoma: 400 mg once daily (continue until disease progression or unacceptable toxicity)
Dosage adjustment for intolerance: Reduce dose to 300 mg once daily; may further reduce to 300 mg daily for 5 consecutive days per week
In clinical trials, treatment was withheld for grade 4 anemia or thrombocytopenia or other grade 3 or 4 drug related toxicity, until resolved to ≤ grade 1. Therapy was reinitiated with dose modification.

Dietary Considerations

Take with food.

Monitoring Parameters

CBC with differential and serum chemistries, including calcium, magnesium, potassium, glucose and creatinine (baseline, then every 2 weeks for 2 months, then monthly), fluid status. Baseline and periodic ECGs were done in clinical trials.

Administration

Administer with food. Do not open, crush, or chew capsules. Maintain adequate hydration (·2 L/day fluids) during treatment.

Dosage Forms: 100 mg capsules

12.3. Gemcitabine

Therapeutic Category: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Adverse Reactions

Frequency of adverse reactions reported for single-agent use of gemcitabine only.
>10%:
Cardiovascular: Peripheral edema (20%), edema (13%)
Central nervous system: Fever (38% to 41%), somnolence (11%)
Dermatologic: Rash (28% to 30%), alopecia (15% to 16%), pruritus (13%)
Gastrointestinal: Nausea/vomiting (69% to 71%; grade 3: 10% to 13%; grade 4: 1% to 2%), diarrhea (19% to 30%), stomatitis (10% to 11%)
Hematologic: Anemia (68% to 73%; grade 4: 1% to 2%), leukopenia (62% to 64%; grade 4: ·1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 36%; grade 4: ·1%), hemorrhage (4% to 17%; grades 3: ·2%; grade 4: <1%); myelosuppression is the dose-limiting toxicity
Hepatic: AST increased (67% to 78%; grade 3: 6% to 12%; grade 4: 2% to 5%), alkaline phosphatase increased (55% to 77%; grade 3: 7% to 16%; grade 4: 2% to 4%), ALT increased (68% to 72%; grade 3: 8% to 10%; grade 4: 1% to 2%), bilirubin increased (13% to 26%; grade 3: 2% to 6%; grade 4: ·2%)
Renal: (32% to 45%; grades 3/4: <1%), hematuria (23% to 35%; grades 3/4: <1%), BUN increased (15% to 16%)
Respiratory: Dyspnea (10% to 23%)
Miscellaneous: Flu-like syndrome (19%), infection (10% to 16%; grade 3: 1% to 2%; grade 4: <1%)
1% to 10%:
Local: Injection site reactions (4%)
Neuromuscular & skeletal: Paresthesia (10%)
Renal: Creatinine increased (6% to 8%)

Respiratory: Bronchospasm (<2%)
<1% (postmarketing and/or case reports):
Adult respiratory distress syndrome, anaphylactoid reaction, anorexia, arrhythmias, arthralgia, bullous skin eruptions, cellulitis, cerebrovascular accident, CHF, chills, constipation, cough, desquamation, diaphoresis, gangrene, GGT increased, headache, hemolytic uremic syndrome (HUS), hepatotoxicity (rare), hyperglycemia, hyper-/hypotension, hypermagnesemia, hypocalcemia, insomnia, interstitial pneumonitis, liver failure, malaise, MI, myalgia, neuropathy, peripheral vasculitis, petechiae, pulmonary edema, pulmonary fibrosis, radiation recall, renal failure, respiratory failure, rhinitis, sepsis, supraventricular arrhythmia, veno-occlusive liver disease, weakness

Drug Interactions

BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X: Avoid combination
Bleomycin: Gemcitabine may enhance the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity may be increased. Risk D: Consider therapy modification
Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. Risk C: Monitor therapy
Echinacea: May diminish the therapeutic effect of Immunosuppressants. Risk D: Consider therapy modification
Fluorouracil: Gemcitabine may increase the serum concentration of Fluorouracil. Risk C: Monitor therapy
Fluorouracil (Systemic): Gemcitabine may increase the serum concentration of Fluorouracil (Systemic). Risk C: Monitor therapy
Fluorouracil (Topical): Gemcitabine may increase the serum concentration of Fluorouracil (Topical). Risk C: Monitor therapy
Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. Risk D: Consider therapy modification
Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. Risk X: Avoid combination
Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. Risk X: Avoid combination
Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. Risk C: Monitor therapy
Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. Risk C: Monitor therapy
Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Risk C: Monitor therapy
Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. Risk X: Avoid combination

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Mechanism of Action

A pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, specific for the S-phase of the cycle. Gemcitabine is phosphorylated intracellularly by deoxycytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase; gemcitabine triphosphate incorporates into DNA and inhibits DNA polymerase.

Pharmacodynamics/Kinetics

Distribution: Infusions <70 minutes: 50 L/m2; Long infusion times (70-285 minutes): 370 L/m2
Protein binding: Low
Metabolism: Metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleoside metabolites
Half-life elimination:
Gemcitabine: Infusion time ·70 minutes: 42-94 minutes; infusion time 3-4 hours: 4-10.5 hours
Metabolite (gemcitabine triphosphate), terminal phase: 1.7-19.4 hours
Time to peak, plasma: 30 minutes after completion of infusion
Excretion: Urine (92% to 98%; primarily as inactive uracil metabolite); feces (<1%)

Dosage

Details concerning dosing in combination regimens should also be consulted. Note: Prolongation of the infusion time >60 minutes and administration more frequently than once weekly have been shown to increase toxicity. I.V.:
Children (refer to specific references for ages of populations studied):
Germ cell tumor, refractory (unlabeled use): 1000 mg/m2/dose days 1, 8, and 15 every 4 weeks (in combination with paclitaxel).
Hodgkin's lymphoma, relapsed (unlabeled use): 1000 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with vinorelbine) or 800 mg/m2 days 1 and 4; repeat cycle every 21 days (in combination with ifosfamide, mesna, vinorelbine, and prednisolone).
Sarcomas (unlabeled use):
Ewing's sarcoma, refractory: 675 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with docetaxel).
Osteosarcoma, refractory: 675 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) or 1000 mg/m2 weekly for 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks.
Adults:
Pancreatic cancer, locally advanced or metastatic: Initial: 1000 mg/m2 weekly for up to 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks.
Dose adjustment: Patients who complete an entire cycle of therapy may have the dose in subsequent cycles increased by 25% as long as the absolute granulocyte count (AGC) nadir is >1500 x 10^6/L, platelet nadir is >100,000 x 10^6/L, and nonhematologic toxicity is less than WHO Grade 1. If the increased dose is tolerated (with the same parameters) the dose in subsequent cycles may again be increased by 20%.
Pancreatic cancer, advanced (unlabeled dosing/combinations): 1000 mg/m2 weekly for up to 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks (in combination with erlotinib) or 1000 mg/m2 days 1, 8, and 15 every 4 weeks (in combination with capecitabine) or 1000 mg/m2 days 1 and 15 every 4 weeks (in combination with cisplatin) or

1000 mg/m2 every 2 weeks (in combination with oxaliplatin).
Nonsmall cell lung cancer (in combination with cisplatin): 1000 mg/m2 days 1, 8, and 15; repeat cycle every 28 days or 1250 mg/m2 days 1 and 8; repeat cycle every 21 days
Breast cancer, metastatic: 1250 mg/m2 days 1 and 8; repeat cycle every 21 days in combination with paclitaxel or (unlabeled dosing) as a single agent: 800 mg/m2 days 1, 8, and 15 of a 28-day treatment cycle.
Ovarian cancer, advanced: 1000 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with carboplatin)
Biliary tract cancer, advanced (unlabeled use): 1000 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with cisplatin) or 1000 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with capecitabine) or 1000 mg/m2 over 100 minutes every 2 weeks (in combination with oxaliplatin).
Bladder cancer (unlabeled use):
I.V.: 1000 mg/m2 once weekly for 3 weeks; repeat cycle every 4 weeks (in combination with cisplatin).
Intravesicular instillation: 2000 mg (in 100 mL NS; retain for 1 hour) twice weekly for 3 weeks; repeat cycle every 4 weeks for at least 2 cycles.
Cervical cancer, recurrent or persistent (unlabeled use): 1000 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with cisplatin) or 1250 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with cisplatin) or 800 mg/m2 days 1, 8, and 15; repeat cycle every 28 days (as a single-agent).
Head and neck cancer, nasopharyngeal (unlabeled use): 1000 mg/m2 days 1, 8, and 15 every 4 weeks.
Hodgkin's lymphoma, relapsed (unlabeled use): 1000 mg/m2 (800 mg/m2 for post-transplant patients) days 1 and 8; repeat cycle every 21 days (in combination with vinorelbine and doxorubicin liposomal) or 800 mg/m2 days 1 and 4; repeat cycle every 21 days (in combination with ifosfamide, mesna, vinorelbine, and prednisolone).
Malignant pleural mesothelioma (unlabeled use; in combination with cisplatin): 1000 mg/m2/dose days 1, 8 and 15 every 4 weeks or 1250 mg/m2/dose days 1 and 8 every 3 weeks.

Non-Hodgkin's lymphoma, refractory (unlabeled use): 1000 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with cisplatin and dexamethasone) or 1000 mg/m2 every 15-21 days (in combination with oxaliplatin and rituximab).

Sarcoma (unlabeled uses):

Ewing's sarcoma, refractory: 675 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with docetaxel).

Osteosarcoma, refractory: 675 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) or 1000 mg/m2 weekly for 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks.

Soft tissue sarcoma, advanced: 800 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with vinorelbine) or 675 mg/m2 days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) or 900 mg/m2 days 1 and 8; repeat cycle every 21 days (fixed dose rate infusion; in combination with docetaxel).

Small cell lung cancer, refractory or relapsed (unlabeled use): 1000-1250 mg/m2 days 1, 8, and 15 every 4 weeks (as a single agent).

Testicular cancer, refractory germ cell (unlabeled use): 1000 mg/m2 days 1 and 8 every 3 weeks (in combination with oxaliplatin) or 1250 mg/m2 days 1 and 8 every 3 weeks (in

combination with oxaliplatin) or 1000 mg/m2/dose days 1, 8, and 15 every 4 weeks (combined with paclitaxel).

Unknown-primary, adenocarcinoma (unlabeled use): 1250 mg/m2 days 1 and 8 every 3 weeks (combined with cisplatin) or 1000 mg/m2 days 1 and 8 every 3 weeks (combined with docetaxel).

Uterine cancer (unlabeled use): 900 mg/m2 days 1 and 8 every 3 weeks (in combination with docetaxel) or 1000 mg/m2 days 1, 8, and 15 every 4 weeks.

Monitoring Parameters
CBC with differential and platelet count (prior to each dose); hepatic and renal function (prior to initiation of therapy and periodically, thereafter); monitor electrolytes, including potassium, magnesium, and calcium (when in combination therapy with cisplatin)

Administration
Infuse over 30 minutes. Note: Prolongation of the infusion time > 60 minutes has been shown to increase toxicity (some unlabeled protocols may include infusion times > 30 minutes). Gemcitabine is being investigated in clinical trials for fixed dose rate (FDR) infusion administration at doses from 1000-2200 mg/m2 at a rate of 10 mg/m2/minute. Prolonged infusion times increase the accumulation of the active metabolite, gemcitabine triphosphate. Patients who receive gemcitabine FDR experience more grade 3/4 hematologic toxicity.

For intravesicular (bladder) instillation, gemcitabine was diluted in 50-100 mL normal saline; patients were instructed to retain in the bladder for 1 hour.

Dosage Forms
Powder for injection, lyophilized: 20 mg/mL (200-mg and 1000-mg vial)

12.4. Busulfan

Therapeutic Classification: Antineoplastic Alkylating agent
Adverse reactions
Intravenous:
>10%:
Cardiovascular: Tachycardia (44%), hypertension (36%; grades 3/4: 7%), edema (28% to 79%), thrombosis (33%), chest pain (26%), vasodilation (25%), hypotension (11%; grades 3/4: 3%)
Central nervous system: Insomnia (84%), fever (80%), anxiety (72% to 75%), headache (69%), chills (46%), pain (44%), dizziness (30%), depression (23%), confusion (11%)
Dermatologic: Rash (57%), pruritus (28%), alopecia (2% to 15%)
Endocrine & metabolic: Hypomagnesemia (77%), hyperglycemia (66%; grades 3/4: 15%), hypokalemia (64%), hypocalcemia (49%), hypophosphatemia (17%)
Gastrointestinal: Nausea (98%), mucositis/stomatitis (97%; grades 3/4: 26%), vomiting (43% to 95%), anorexia (85%), diarrhea (84%; grades 3/4: 5%), abdominal pain (72%), dyspepsia (44%), constipation (38%), xerostomia (26%), rectal disorder (25%), abdominal fullness (23%)
Hematologic: Myelosuppression (≤100%), neutropenia (100%; median recovery: 13 days), thrombocytopenia (98%; median onset: 5-6 days), lymphopenia (children: 79%), anemia (69%)
Hepatic: Hyperbilirubinemia (49%; grades 3/4: 30%), ALT increased (31%; grades 3/4: 7%), veno-occlusive disease (adults: 8% to 12%; children: 21%), jaundice (12%)
Local: Injection site inflammation (25%), injection site pain (15%)
Neuromuscular & skeletal: Weakness (51%), back pain (23%), myalgia (16%), arthralgia (13%)
Renal: Creatinine increased (21%), oliguria (15%)

Respiratory: Rhinitis (44%), lung disorder (34%), cough (28%), epistaxis (25%), dyspnea (25%), pneumonia (children: 21%), hiccup (18%), pharyngitis (18%)
Miscellaneous: Infection (51%), allergic reaction (26%)
1% to 10%:
Cardiovascular: Arrhythmia (5%), cardiomegaly (5%), atrial fibrillation (2%), ECG abnormal (2%), heart block (2%), heart failure (grade 3/4: 2%), pericardial effusion (2%), tamponade (children with thalassemia: 2%), ventricular extrasystoles (2%), hypervolemia
Central nervous system: Lethargy (7%), hallucination (5%), agitation (2%), delirium (2%), encephalopathy (2%), seizure (2%), somnolence (2%), cerebral hemorrhage (1%)
Dermatologic: Vesicular rash (10%), vesiculobullous rash (10%), skin discoloration (8%), maculopapular rash (8%), acne (7%), exfoliative dermatitis (5%), erythema nodosum (2%)
Endocrine & metabolic: Hyponatremia (2%)
Gastrointestinal: Ileus (8%), weight gain (8%), hematemesis (2%), pancreatitis (2%)
Hematologic: Prothrombin time increased (2%)
Hepatic: Hepatomegaly (6%)
Renal: Hematuria (8%), dysuria (7%), hemorrhagic cystitis (grade 3/4: 7%), BUN increased (3%)
Respiratory: Asthma (8%), alveolar hemorrhage (5%), hyperventilation (5%), hemoptysis (3%), pleural effusion (3%), sinusitis (3%), atelectasis (2%), hypoxia (2%)
Oral: Frequency not defined:
Central nervous system: Seizure
Dermatologic: Hyperpigmentation of skin (busulfan tan 5% to 10%), alopecia, rash, urticaria
Endocrine & metabolic: Amenorrhea, ovarian suppression
Hematologic: Myelosuppression (anemia, leukopenia, thrombocytopenia), pancytopenia
I.V. and/or Oral: Infrequent, postmarketing, and/or case reports: Acute leukemias, adrenal suppression, alopecia (permanent), aplastic anemia (may be irreversible), azoospermia, blurred vision, cataracts, cheilosis, cholestatic jaundice, corneal thinning, dry skin, endocardial fibrosis, erythema multiforme, erythema nodosum, esophageal varices, gynecomastia, hemorrhagic cystitis, hepatic dysfunction, hepatocellular atrophy, hyperuricemia, hyperuricosuria, interstitial pulmonary fibrosis (busulfan lung; manifested by a diffuse interstitial pulmonary fibrosis and persistent cough, fever, rales, and dyspnea; may be relieved by corticosteroids); malignant tumors, myasthenia gravis, ocular (lens) changes, ovarian failure, porphyria cutanea tarda, radiation myelopathy, radiation recall (skin rash), sepsis, sterility, testicular atrophy
Metabolism/Transport Effects
Substrate of CYP3A4 (major)
Drug Interactions
Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Busulfan. Risk C: Monitor therapy
BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X: Avoid combination
Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Management: Upon completion/discontinuation of conivaptan, allow at least 7 days before initiating therapy with drugs that are CYP3A4 substrates. Risk D: Consider therapy modification
CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy
CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy
CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. Risk D: Consider therapy modification
Dasatinib: May increase the serum concentration of CYP3A4 Substrates. Risk C: Monitor

therapy
Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy
Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. Risk C: Monitor therapy
Echinacea: May diminish the therapeutic effect of Immunosuppressants. Risk D: Consider therapy modification
Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy
Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. Risk D: Consider therapy modification
MetroNIDAZOLE: May increase the serum concentration of Busulfan. Risk D: Consider therapy modification
MetroNIDAZOLE (Systemic): May increase the serum concentration of Busulfan. Risk D: Consider therapy modification
Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. Risk X: Avoid combination

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. Risk X: Avoid combination
Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. Risk C: Monitor therapy
Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. Risk C: Monitor therapy
Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Risk C: Monitor therapy
Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. Risk X: Avoid combination
Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol due to GI irritation.
Food: No clear or firm data on the effect of food on busulfan bioavailability.
Herb/Nutraceutical: Avoid St John's wort (may decrease busulfan levels).

Mechanism of Action

Busulfan is an alkylating agent which reacts with the N-7 position of guanosine and interferes with DNA replication and transcription of RNA. Busulfan has a more marked effect on myeloid cells than on lymphoid cells and is also very toxic to hematopoietic stem cells. Busulfan exhibits little immunosuppressive activity. Interferes with the normal function of DNA by alkylation and

cross-linking the strands of DNA.

Pharmacodynamics/Kinetics

Duration: 28 days

Absorption: Rapid and complete

Distribution: V_d: ~1 L/kg; into CSF and saliva with levels similar to plasma

Protein binding: 32% to plasma proteins and 47% to red blood cells

Metabolism: Extensively hepatic (may increase with multiple doses); glutathione conjugation followed by oxidation

Half-life elimination: After first dose: 3.4 hours; After last dose: 2.3 hours

Time to peak, serum: Oral: Within 4 hours; I.V.: Within 5 minutes

Excretion: Urine (10% to 50% as metabolites) within 24 hours (<2% as unchanged drug)

Dosage

Note: Premedicate with prophylactic anticonvulsant therapy (e.g., phenytoin) prior to high-dose busulfan treatment.

Children:

CML, remission induction: Oral: 0.06-0.12 mg/kg/day or 1.8-4.6 mg/m2/day; titrate dosage to maintain leukocyte count above 40,000/mm3; reduce dosage by 50% if the leukocyte count reaches 30,000-40,000/mm3; discontinue drug if counts fall to ·20,000/mm3

BMT marrow-ablative conditioning regimen:

Oral: 1 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

I.V.:

≤12 kg: 1.1 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

>12 kg: 0.8 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

Adjust dose to desired AUC [1125 μmol(min)] using the following formula:

Adjusted dose (mg) = Actual dose (mg) x [target AUC μmol(min) / actual AUC μmol(min)]

Adults:

CML, remission induction: Oral: 60 mcg/kg/day or 1.8 mg/m2/day; usual range: 4-8 mg/day (may be as high as 12 mg/day); Maintenance doses: 1-4 mg/day to 2 mg/week to maintain WBC 10,000-20,000 cells/mm3

BMT marrow-ablative conditioning regimen:

Oral: 1 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

I.V.: 0.8 mg/kg (ideal body weight or actual body weight, whichever is lower); for obese or severely-obese patients adjusted ideal body weight is recommended) every 6 hours for 4 days (a total of 16 doses)

Polycythemia vera (unlabeled use): Oral: 2-6 mg/day

Thrombocytosis (unlabeled use): Oral: 4-6 mg/day

Monitoring Parameters

CBC with differential and platelet count, liver function tests (evaluate transaminases, alkaline phosphatase, and bilirubin daily for at least 28 days post transplant)

Administration

Intravenous busulfan should be administered as a 2-hour via central line.

BMT only: To facilitate ingestion of high oral doses, insert multiple tablets into gelatin capsules.

Dosage Forms

Injection: 6 mg/mL (10 mL)

Suspension, oral: 2 mg/mL (MDACC compounded product)

Tablet: 2 mg

12.5. Melphalan

Therapeutic Category: Antineoplastic Agent, Alkylating Agent

Adverse Reactions

>10%:

Gastrointestinal: Nausea/vomiting (oral low-dose: <10%; I.V.: 30% to 90%), oral ulceration
Hematologic: Myelosuppression, leukopenia (nadir: 14-21 days; recovery: 28-35 days), thrombocytopenia (nadir: 14-21 days; recovery: 28-35 days), anemia
Miscellaneous: Secondary malignancy (<2% to 20%; cumulative dose and duration dependent, includes acute myeloid leukemia, myeloproliferative syndrome, carcinoma)

1% to 10%: Miscellaneous: Hypersensitivity (I.V.: 2%; includes bronchospasm, dyspnea, edema, hypotension, pruritus, rash, tachycardia, urticaria)

Infrequent, frequency undefined, postmarketing, and/or case reports: Agranulocytosis, allergic reactions, alopecia, amenorrhea, anaphylaxis (rare), bladder irritation, bone marrow failure (irreversible), BUN increased, cardiac arrest, diarrhea, encephalopathy, hemolytic anemia, hemorrhagic cystitis, hemorrhagic necrotic enterocolitis, hepatic veno-occlusive disease (I.V. melphalan), hepatitis, injection site reactions (ulceration, necrosis), interstitial pneumonitis, jaundice, ovarian suppression, pruritus, pulmonary fibrosis, radiation myelopathy, rash (maculopapular), seizure, SIADH, skin hypersensitivity, skin vesiculation, sterility, stomatitis, testicular suppression, tingling sensation, transaminases increased, vasculitis, warmth sensation

Drug Interactions

BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X: Avoid combination
Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. Exceptions: Digitoxin. Risk C: Monitor therapy
Carmustine: Melphalan may enhance the adverse/toxic effect of Carmustine. Specifically, melphalan may sensitize patients to carmustine lung toxicity. Risk C: Monitor therapy
CycloSPORINE: Melphalan may enhance the nephrotoxic effect of CycloSPORINE. Risk C: Monitor therapy
CycloSPORINE (Systemic): Melphalan may enhance the nephrotoxic effect of CycloSPORINE (Systemic). Risk C: Monitor therapy
Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. Risk C: Monitor therapy
Echinacea: May diminish the therapeutic effect of Immunosuppressants. Risk D: Consider therapy modification
Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. Risk D: Consider therapy modification
Nalidixic Acid: May enhance the adverse/toxic effect of Melphalan. Necrotic enterocolitis has been reported in pediatric patients. Risk X: Avoid combination
Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. Risk X: Avoid combination
Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. Risk X: Avoid combination
Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. Risk C: Monitor therapy

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. Risk C: Monitor therapy
Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Risk C: Monitor therapy
Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. Risk X: Avoid combination
Vitamin K Antagonists (e.g., warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).
Food: Food interferes with oral absorption.

Mechanism of Action

Alkylating agent which is a derivative of mechlorethamine that inhibits DNA and RNA synthesis via formation of carbonium ions; cross-links strands of DNA; acts on both resting and rapidly dividing tumor cells.

Pharmacodynamics/Kinetics

Note: Pharmacokinetics listed are for FDA-approved doses.
Absorption: Oral: Variable and incomplete
Distribution: V_d: 0.5-0.6 L/kg throughout total body water; low penetration into CSF
Protein binding: 60% to 90%; primarily to albumin, 20% to α1-acid glycoprotein
Metabolism: Hepatic; chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan
Bioavailability: Unpredictable; 61% ± 26%, decreasing with repeated doses
Half-life elimination: Terminal: I.V.: 75 minutes; Oral: 1-2 hours
Time to peak, serum: ~1-2 hours
Excretion: Oral: Feces (20% to 50%); urine (~10% as unchanged drug)

Dosage

Details regarding dosing in combination regimens should also be consulted.
Oral: Adults (adjust dose based on patient response and weekly blood counts):
Multiple myeloma (palliative treatment): Note: Response is gradual; may require repeated courses to realize benefit:
Usual dose (as described in the manufacturer's labeling):
6 mg once daily for 2-3 weeks initially, followed by up to 4 weeks rest, then a maintenance dose of 2 mg daily as hematologic recovery begins or
10 mg daily for 7-10 days; institute 2 mg daily maintenance dose after WBC >4000 cells/mm3 and platelets >100,000 cells/mm3 (~4-8 weeks); titrate maintenance dose to hematologic response or
0.15 mg/kg/day for 7 days, with a 2-6 week rest, followed by a maintenance dose of ·0.05 mg/kg/day as hematologic recovery begins or
0.25 mg/kg/day for 4 days (or 0.2 mg/kg/day for 5 days); repeat at 4- to 6-week intervals as ANC and platelet counts return to normal
Other dosing regimens in combination therapy (unlabeled doses):
4 mg/m2/day for 7 days every 4 weeks or
6 mg/m2/day for 7 days every 4 weeks or
0.25 mg/kg/day for 4 days every 6 weeks or

9 mg/m2/day for 4 days every 6 weeks
Ovarian carcinoma: 0.2 mg/kg/day for 5 days, repeat every 4-5 weeks or
Unlabeled dosing: 7 mg/m2/day in 2 divided doses for 5 days, repeat every 28 days
Amyloidosis (unlabeled use): 0.22 mg/kg/day for 4 days every 28 days in combination with oral dexamethasone.

I.V.:

Children (unlabeled use): Conditioning regimen for autologous hematopoietic stem cell transplantation:
140 mg/m2 2 days prior to transplantation (combined with busulfan) or
180 mg/m2 (with pre- and posthydration) 12-30 hours prior to transplantation or
45 mg/m2/day for 4 days starting 8 days prior to transplantation (combined with busulfan or etoposide and carboplatin)
Adults:
Multiple myeloma (palliative treatment): 16 mg/m2 administered at 2-week intervals for 4 doses, then administer at 4-week intervals after adequate hematologic recovery.
Conditioning regimen for autologous hematopoietic stem cell transplantation (unlabeled use):
200 mg/m2 alone 2 days prior to transplantation or
140 mg/m2 2 days prior to transplantation (combined with busulfan) or
140 mg/m2 2 days prior to transplantation (combined with total body irradiation [TBI]) or
140 mg/m2 5 days prior to transplantation (combined with TBI)
Hodgkin's disease (unlabeled use): 30 mg/m2 on day 6 of combination chemotherapy (mini-BEAM) regimen
Elderly: Refer to adult dosing; use caution and begin at the lower end of dosing range

Monitoring Parameters

CBC with differential and platelet count, serum electrolytes, serum uric acid

Administration

Oral: Administer on an empty stomach (1 hour prior to or 2 hours after meals)
Parenteral: Due to limited stability, complete administration of I.V. dose should occur within 60 minutes of reconstitution
I.V.: Infuse over 15-30 minutes. Extravasation may cause local tissue damage; administration by slow injection into a fast running I.V. solution into an injection port or via a central line is recommended; do not administer by direct injection into a peripheral vein.
BMT only: Saline-based hydration preceding (2-4 hours), during, and following (6-12 hours) administration reduces risk of drug precipitation in renal tubules. Hydrolysis causes loss of 1% melphalan injection per 10 minutes.

Dosage Forms

Injection: 50 mg
Tablet: 2 mg

13.0 References

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