DRUG NAME: Dacarbazine

SYNONYM(S): DIC,[1] DTIC[1,2]

COMMON TRADE NAME(S): Dacarbazine for Injection

CLASSIFICATION: alkylating agent[3]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Dacarbazine is a structural analogue of imidazole carboxamide, a purine precursor.[1] Dacarbazine undergoes activation via cytochrome P450 in the liver to the reactive compound, methyltriazenoimidazole carboxamide (MTIC).[4] The cytotoxicity of MTIC is thought to be due primarily to the formation of methylcarbonium ions that attack nucleophilic groups in DNA.[3,5] Dacarbazine may also inhibit DNA and RNA synthesis by acting as a purine analogue and by interacting with sulfhydryl groups.[3,6] Both dacarbazine and temozolomide are prodrugs of MTIC. Dacarbazine is cell cycle phase-nonspecific and is mildly immunosuppressive.[3]

PHARMACOKINETICS:

Oral Absorption	not given orally due to incomplete and variable absorption	
Distribution	cross blood brain barrier?[7]	minimal
	volume of distribution[5]	0.6 L/kg; exceeds total body water, suggesting localization in body tissue, likely the liver
	plasma protein binding	<5%
Metabolism	primarily hepatic, principally via CYP 1A2, secondarily by CYP 2E1; CYP 1A1 may play a role in extrahepatic metabolism[4]	
	active metabolite(s)[4,5,8]	yes; including MTIC
	inactive metabolite(s)[2,4,8]	yes; including aminoimidazole carboxamide (AIC)
Excretion	primarily renal, net tubular secretion (saturable at doses >1200 mg/m^2), minor hepatobiliary and pulmonary excretion[7]	
	urine	20-50% unchanged, 12-24% as AIC
	feces	no information found
	terminal half life[5]	5 h
	clearance[9]	15 mL/kg/min

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:
Lymphoma, Hodgkin's[10]
*Melanoma, metastatic malignant
Sarcoma, soft tissue[11-13]

*Health Canada approved indication

Other uses:
Islet cell carcinoma[5]
Medullary carcinoma of the thyroid[5]
Neuroblastoma[1]

SPECIAL PRECAUTIONS:

Contraindicated in patients who have a history of hypersensitivity reaction to dacarbazine[3] or temozolomide.[14]

Caution: Monitor hepatic and renal function during therapy.[3]

Carcinogenicity: Dacarbazine is carcinogenic in animals.[3]

Mutagenicity: No information found regarding mutagenicity in Ames test and mammalian *in vitro* mutation test.[15] Dacarbazine is clastogenic in mammalian *in vivo* chromosome tests.[16]

Fertility: Does not typically cause more than transient gonadal dysfunction.[17]

Pregnancy: FDA Pregnancy Category C.[5] Animal studies have shown fetal risks and there are no controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk.[3,5]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[18,19] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylaxis (<1%)[5]
blood/bone marrow/ febrile neutropenia	myelosuppression
	leukopenia; typically occurs 14 days after treatment, has occurred as early as 10 days and in 10% of patients is delayed as late as 30 days; typical duration 1 week but 3 weeks has been reported[20]
	thrombocytopenia; typically occurs 12-18 days after treatment, in 10% of patients is delayed until after day 30; typical duration 1 week but 3 weeks has been reported[20]
cardiovascular (arrhythmia)	EKG abnormalities
cardiovascular (general)	orthostatic hypotension; typically associated with doses >850 mg/m^2
constitutional symptoms	fatigue
dermatology/skin	*extravasation hazard: irritant*[21]
	alopecia (1-10%)[5]
	erythematous, macular, papular, and/or urticarial rash (1-10%)[5]
	facial flushing (<1%); transient[1]
	phototoxicity[22] (1-10%)[5]; typically occurs hours after treatment and lasts 1-4 days,[23] self-limiting and does not require drug discontinuation[24]
	reaction resembling fixed drug eruption
gastrointestinal	***emetogenic potential: high***[25]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	anorexia (≥90%); see paragraph following the **Side Effects** table
	diarrhea (<1%); with high-dose,[5] typically not severe
	nausea and vomiting (≥90%); see paragraph following the **Side Effects** table
	stomatitis[1,6]
hepatobiliary/pancreas	hepatotoxicity with hepatocellular necrosis and/or hepatic vascular occlusion (0.01%)[1]; see paragraph following the **Side Effects** table
metabolic/laboratory	elevated liver enzymes[1] (<1%)[5]
neurology	confusion
	facial paresthesia (<1%)[5]; transient[1]
	seizures
ocular/visual	blurred vision
pain	headache (<1%)[5]
	injection site pain; may be minimized by administration via central line or by infusion of diluted solution[1,5]
renal/genitourinary	renal dysfunction
sexual/reproductive function	gonadal dysfunction[17]; transient
syndromes	influenza-like syndrome (<10%); fever, myalgia, and malaise, typically occurs after single large doses 2-7 days after treatment and persists for 7-21 days, may recur, supportive management recommended
vascular	veno-occlusive disease; see paragraph following the **Side Effects** table

Adapted from standard reference[3] unless specified otherwise.

Nausea, vomiting, and anorexia occur in ≥90% of patients receiving dacarbazine. GI symptoms are most common with initial doses, with tolerance developing after the first few days of successive treatment when the drug is given on a 5 day schedule.[3,7] Nausea and vomiting are typically acute in onset, intense and short-lived, persisting for 1-12 hours.[3] Restriction of food and fluid intake 4-6 h prior to treatment has been recommended.[3] Antiemetic agents are required for prophylaxis and treatment of N/V. (Refer to SCNAUSEA protocol.) Intractable nausea and vomiting requiring drug discontinuation has rarely occurred.[1,3]

Hepatotoxicity with hepatocellular necrosis and/or hepatic vascular occlusion: Vascular occlusion typically occurs during the second cycle of treatment and may be preceded by mild, transient hepatic toxicity after the first cycle.[3] Eosinophilia and eosinophilic infiltrates have been reported with hepatic vascular occlusion, suggesting that a hypersensitivity mechanism may be involved. Fatalities due to dacarbazine-induced hepatotoxicity have occurred.[3] Hepatotoxicity may be more common with combination chemotherapy.[1,5] Monitor hepatic function during therapy.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aldesleukin[3]	decreased therapeutic effect of dacarbazine	related to aldesleukin dose; increased clearance (~38%) and volume of distribution (~36%) of dacarbazine	usual monitoring; dacarbazine dosage increase may be required

AGENT	EFFECT	MECHANISM	MANAGEMENT
aldesleukin[26]	hypersensitivity reactions have been reported when used concurrently	unknown	usual monitoring
levodopa[3,26]	reduced response to levodopa	unknown; unlikely due to pharmacokinetic changes	usual monitoring; levodopa dosage increase may be required

Dacarbazine inhibits xanthine oxidase and may theoretically potentiate the activity and toxicity of mercaptopurine and azathioprine.[3]

Dacarbazine inhibits xanthine oxidase and may theoretically potentiate the activity, but not the toxicity, of allopurinol.[3]

The principle liver enzyme responsible for dacarbazine metabolism in humans is CYP 1A2, but CYP 2E1 may participate when CYP 1A2 expression is low. CYP 1A1 is found in extrahepatic tissue and may also contribute to the metabolism of dacarbazine at its site of action.[4] Theoretically, inducers of these enzymes may increase the metabolism of dacarbazine along these pathways, decreasing dacarbazine serum levels, but increasing the serum levels and effects of its metabolites. Conversely, inhibitors of these enzymes may decrease the metabolism of dacarbazine along these pathways, increasing serum levels of dacarbazine, but decreasing the serum levels and effects of its metabolites.[27]. Clinical significance of these interactions is unknown. Monitor for therapeutic activity of treatment and presentation of side effects during concurrent therapy.[27]

SUPPLY AND STORAGE:

Injection: Mayne Pharma (Canada) Inc, supplies dacarbazine as 200 mg and 600 mg vials. Store in the refrigerator and protect from light.[3]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: Dacarbazine is sensitive to light and heat; a change in colour from pale ivory to pink is a sign of decomposition.[1] Protect from light to preserve activity and prevent formation of inactive and potentially harmful degradation products.[28]

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	***over at least 1 minute***[1,3] into tubing of running IV; see ***Prevention and Management of Extravasation of Chemotherapy***. Intermittent infusion typically less painful than direct IV.
Intermittent infusion	***over 1-2 h,***[10,11,29] over 15-30 minutes has been used[1,3] Rapid infusion may cause severe venous irritation.[1,5] If irritation occurs, slow the rate of infusion.
Continuous infusion	no information found
Intraperitoneal	no information found

BCCA administration guideline noted in ***bold***, ***italics***

Intrapleural	no information found
Intrathecal	investigational; has been used[30]
Intra-arterial	investigational; has been used[1,5]
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: ***3 weeks***[5,12,13]***:***	***850 mg/m^2 IV for one dose on day 1*** (total dose per cycle 850 mg/m^2)
	4 weeks[10]***:***	***375 mg/m^2 IV for one dose on day 1 and 15*** (total dose per cycle 750 mg/m^2)
	3 weeks[3]:	2-4.5 mg/kg IV once daily for 10 consecutive days starting on day 1 (total dose per cycle 20-45 mg/kg)
	3-4 weeks[3,5]:	100-250 mg/m^2 IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 500-1250 mg/m^2)
High-dose therapy:	***3-4 weeks***[5,11,18,29]***:***	***rarely used in doses exceeding 1.2 g/m^2***
Intra-arterial:	n/a[5]:	50-400 mg/m^2 IV for 5-10 days (total dose per cycle 250-4000 mg/m^2)
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	adjustment required, no details found[3,5]	
Dosage in hepatic failure:	adjustment required,[3] no details found; alternatively may monitor for toxicity[5]	
Dosage in dialysis:	no information found	

Children:

Intravenous:	Cycle Length: safety and efficacy have not been established in children[3]; dacarbazine has been used in pediatric patients[5,31]	
	4 weeks[5,31]:	375 mg/m^2 IV for one dose on day 1 and 15 (total dose per cycle 750 mg/m^2)

3-4 weeks[5,31,32]:	200-470 mg/m^2 IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 1000-2350 mg/m^2)
3-4 weeks[5,31]:	800-900 mg/m^2 IV for one dose on day 1 (total dose per cycle 800-900 mg/m^2)

REFERENCES:

1. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1007-1009.
2. DRUGDEX® Evaluations (database on the Internet). Dacarbazine. Thomson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 26 April 2007.
3. Mayne Pharma (Canada) Inc. DACARBAZINE FOR INJECTION product monograph. Montreal, Quebec; 25 July 2003.
4. Reid JM, Kuffel MJ, Miller JK, et al. Metabolic activation of dacarbazine by human cytochromes P450: the role of CYP1A1, CYP1A2, and CYP2E1. Clin Cancer Res 1999;5(8):2192-2197.
5. Rose BD editor. Dacarbazine. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 15.1; 2007.
6. USPDI® Drug Information for the Health Care Professional (database on the Internet). Dacarbazine (Systemic). Thompson MICROMEDEX®, 2007. Available at: www.micromedex.com. Accessed 26 April 2007.
7. Chabner BA, Longo DL. Cancer chemotherapy and biotherapy. 4th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006. p. 317-320.
8. Pizzo P, Poplack D. Principles and practice of pediatric oncology. 5th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006. p. 316-317.
9. Breithaupt H, Dammann A, Aigner K. Pharmacokinetics of dacarbazine (DTIC) and its metabolite 5-aminoimidazole-4-carboxamide (AIC) following different dose schedules. Cancer Chemother Pharmacol 1982;9(2):103-109.
10. BC Cancer Agency Lymphoma Tumour Group. (LYABVD) BCCA Protocol Summary for Treatment of Hodgkin's Disease with Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine. Vancouver, British Columbia: BC Cancer Agency; 1 February 2007.
11. BC Cancer Agency Sarcoma Tumour Group. (SADTIC) BCCA Protocol Summary for High Dose Single Agent Dacarbazine (DTIC) for Metastatic Soft Tissue Sarcoma. Vancouver, British Columbia: BC Cancer Agency; 1 April 2000.
12. BC Cancer Agency Sarcoma Tumour Group. (SAAVADIC) BCCA Protocol Summary for ADRIAMYCIN® and DTIC Program for use in Patients with Soft Tissue Sarcoma. Vancouver, British Columbia: BC Cancer Agency; 1 August 2003.
13. BC Cancer Agency Sarcoma Tumour Group. (SAAJADIC) BCCA Protocol Summary for Doxorubicin (ADRIAMYCIN®) and Dacarbazine (DTIC) Program for Patients with Soft Tissue Sarcoma. Vancouver, British Columbia: BC Cancer Agency; 1 November 1999.
14. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1192-1193.
15. Chabner BA, Longo DL. Cancer chemotherapy and biotherapy. 4th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006. p. 73-75.
16. Miele M, Bonassi S, Bonatti S, et al. Micronucleus analysis in peripheral blood lymphocytes from melanoma patients treated with dacarbazine. Anticancer Res 1998;18(3B):1967-71.
17. REPROTOX® (database on the Internet). Dacarbazine. Thomson MICROMEDEX®, 2007. Available at: http://www.micromedex.com/. Accessed May 4, 2007.
18. Kenneth Wilson MD. Personal communication. BCCA Melanoma Tumour Group; 7 June 2007.
19. Meg Knowling MD. Personal communication. BCCA Sarcoma Tumour Group; 19 June 2007.
20. Hospira Healthcare Corporation. Dacarbazine for Injection® product monograph. Saint-Laurent, Quebec; 4 June 2007.
21. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.
22. Allen JE. Drug-induced photosensitivity. Clinical Pharmacy 1993;12(8):580-587.
23. Serrano G, Aliaga A, Febrer I, et al. Dacarbazine-induced photosensitivity. Photodermatol 1989;6(3):140-141.
24. Yung CW, Winston EM, Lorincz AL. Dacarbazine-induced photosensitivity reaction. J Am Acad Dermatol 1981;4(5):541-543.
25. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
26. Drug Interaction Facts (database on the Internet). Dacarbazine Cancer Chemo Manual. Facts and Comparisons 4.0, Available at: http://online.factsandcomparisons.com. Accessed April 26, 2007.
27. Basow DS. Lexi-Interact™ Online Dacarbazine. UpToDate 18.1, Available at: www.uptodate.com. Accessed 22 June 2010.
28. El Aatmani M, Poujol S, Astre C, et al. Stability of dacarbazine in amber glass vials and polyvinyl chloride bags. Am J Health-Syst Pharm 2002;59(14):1351-6.
29. BC Cancer Agency Melanoma Tumour Group. (SMDTIC) BCCA Protocol Summary for Palliative Therapy for Metastatic Malignant Melanoma Using High Dose Dacarbazine (DTIC). Vancouver, British Columbia: BC Cancer Agency; 1 December 2003.
30. Champagne MA, Silver HKB. Intrathecal dacarbazine treatment of leptomeningeal malignant melanoma. J Natl Cancer Inst 1992;84(15):1203-1204.

31. Rose BD editor. Dacarbazine: Pediatric drug information. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 15.1; 2007.
32. Pizzo P, Poplack D. Principles and practice of pediatric oncology. 5th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006. p. 300.