Drug Monograph

A - Drug Name

dacarbazine

SYNONYM(S): DTIC

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B - Mechanism of Action and Pharmacokinetics

Dacarbazine is an imidazole carboxamide derivative with structural similarity to certain purines; however, its primary mode of action appears to be alkylation of nucleic acids. Inhibition of DNA synthesis, by acting as a purine analogue and interacting with sulfhydryl groups, is also possible. Dacarbazine is cell cycle non-specific.

Distribution	Liver. Pharmacokinetics may be more than dose-dependent at high doses (>1200 mg/m^2) due to decreased renal clearance; metabolism may also be saturated at this level.	
	Cross blood brain barrier?	< 15 %
	PPB	< 5 %
Metabolism	Metabolized by hepatic microsomal enzyme oxidation system.	
	Active metabolites	Yes
	Inactive metabolites	Yes, including amino imidazole carboxamide (AIC; major)
Elimination	Excreted in urine via renal tubular secretion.	

	Urine	20-50% unchanged, 12-24% as AIC
	Half-life	Terminal t½: 0.5 to 3.5 hours

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C - Indications and Status

Health Canada Approvals:

- Palliative therapy of metastatic malignant melanoma

Other Uses:

- Adrenal cancer (pheochromocytoma)
- Hodgkin lymphoma
- Neuroendocrine tumours

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Irritant

The incidences for the adverse effects are based on product monographs where available. Incidences marked with "^" are based on the dacarbazine arm in other metastatic melanoma clinical trials.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	ECG changes	D
	Flushing (facial; rare)	I
	Hypotension (high doses > 850mg/m2)	I
Dermatological	Alopecia (rare)	E
	Photosensitivity (rare, more common with large single doses)	I
	Rash (rare)	I
Gastrointestinal	Anorexia (>90%)	E

	Constipation (23%) ^	E
	Diarrhea (12%) ^	I
	Mucositis (11%) ^	E
	Nausea, vomiting (>90%)	I
General	Fatigue (31%) ^	E
	Flu-like symptoms (<10%)	E
Hematological	Immunosuppression	E
	Myelosuppression (11%) ^ (neutropenia); may be severe	E
Hepatobiliary	Hepatic necrosis (rare)	E
	↑ LFTs (rare)	E
	Veno-occlusive disease (rare)	E
Hypersensitivity	Hypersensitivity (rarely severe)	I
Injection site	Injection site reaction (pain / irritation)	I
	Phlebitis (chemical)	I
Nervous System	Confusion (rare)	I
	Headache (rare)	E
	Paresthesia (facial; rare)	E
	Seizure (rare)	I
Ophthalmic	Blurred vision (rare)	E
Renal	Creatinine increased (impaired renal function; rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Anorexia, nausea and vomiting appear to be induced via a CNS mechanism. The use of prophylactic antiemetics is recommended. Nausea and vomiting may last 1-12h but tend to subside after the first few days of treatment. In rare cases, this may require drug discontinuation.

A **flu-like syndrome** consisting of fever, myalgia and malaise may occur, especially after large, single doses. These symptoms occur in less than 10% of patients, starting 2-7 days after treatment and lasting for 7-21 days. This syndrome may recur on subsequent treatments.

Hepatotoxicity, including fatal cases, has occurred during dacarbazine treatment. It was usually seen during the second cycle; some cases have been preceded by mild, transient hepatic toxicity after the first cycle.

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E - Dosing

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 white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Adults:

Intravenous: 200-250 mg/m² daily for 5 days Every 3-4 weeks

Intravenous: 2 to 4.5 mg/kg daily for 10 days Every 3 weeks

Intravenous: 375 mg/m² IV on days 1 and 15 (as in ABVD); every 4 weeks

Dosage with Toxicity:

Dosage in myelosuppression:

Modify according to protocol by which patient is being treated. If significant hematological toxicity occurs, consider hold or discontinuation of therapy.

Dosage with Toxicity:

Toxicity	Action[1]	Dose
Grade 3 (with fever or systemic infection) or Grade 4 hematological toxicity	Hold	↓ 25%
Grade 3 non-hematological	Hold	↓ 25%; discontinue if recurs after 2 dose reductions
Grade 4 non-hematological	Discontinue	Not applicable

[1] Before retreatment, major organ toxicities should recover to ≤ Grade 2, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.

Dosage with Hepatic Impairment:

Adjustment required, no details found

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Dose*
>50	100% of dose
30-50	75% of dose
10-30	50% or discontinue
<10	discontinue

* modified from Kintzel et al 1995

Dosage in the elderly:

Safety and efficacy not established.

Children:

Safety and efficacy not established.

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F - Administration Guidelines

- Administration of concentrated dacarbazine solutions may cause severe perivenous pain; therefore, it is recommended to give dacarbazine as a diluted IV infusion.
- Extreme care should be taken to avoid extravasation as this may result in tissue damage and severe pain.
- May be mixed in normal saline or D5W bag (250 to 1000 mL), depending on the regimen.
- Infuse over 30 to 120 minutes; refer to the institutional guidelines for infusion duration.

- Keep dacarbazine vials refrigerated (2 to 8ºC); protect the undiluted drug, infusion bags and tubing from light.

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G - Special Precautions

Contraindications:

- patients with known hypersensitivity to dacarbazine and any component of its formulation
- patients who have previously had severe myelosuppression.

Other Warnings/Precautions:

- Dacarbazine is a moderate immunosuppressive agent. Avoid the use of live vaccines during treatment and for at least 3 months after the last dose. Response to inactivated vaccines may be decreased.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Teratogenicity: Yes
  Dacarbazine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during therapy and for at least 6 months after treatment cessation.
- Breastfeeding:
  Breast feeding is not recommended due to the potential secretion into breast milk.
- Fertility effects: Probable

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H - Interactions

Dacarbazine is metabolized by CYP1A1, CYP1A2 and CYP2E1.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Interleukin-2	↑ dacarbazine clearance	Unknown	Clinical significance is uncertain; increased dose of dacarbazine may be required.

Fotemustine	Fatal Acute Respiratory Distress Syndrome	Unknown	Caution
levodopa	↓ response to levodopa	Unknown	Caution in patients stabilized on levodopa; dosage adjustments of levodopa may be required
Phenytoin, phenobarbital and other drugs inducing hepatic oxidase enzymes.	↑ metabolism of dacarbazine	Induction of hepatic microsomal enzyme oxidation system	Caution; monitor carefully
CYP1A2 inhibitors (e.g., atazanavir, ciprofloxacin, fluvoxamine)	↓ metabolism of dacarbazine	Inhibition of CYP1A2 enzymes	Caution; monitor carefully and consider therapy modification.
CYP2E1 inhibitors (e.g., ritonavir, fluoxetine)	↓ metabolism of dacarbazine	Inhibition of CYP2E1 enzymes	Caution; monitor carefully and consider therapy modification.
Mercaptopurine allopurinol, azathioprine	↑ activity of these drugs	Dacarbazine inhibits xanthine oxidase	Theoretical risk; monitor carefully

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Liver function tests	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Clinical toxicity assessment including GI, infection, bleeding, hypersensitivity, skin, injection site reactions, flu-like symptoms	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

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April 2020 Updated pharmacokinetics, indications, adverse effects, administration guidelines, special precautions, and monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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