GFR is still an elaborate procedure, and may be less accurate in children than adults.[4] Chatelut and colleagues have proposed formulae for determining clearance of carboplatin in both adults[5] and children.[4]

It has been suggested that the Calvert and Chatelut formulae are not sufficiently accurate for use in children, or in adults with very severe renal impairment. Bayesian methods are the technique of choice where serum carboplatin concentrations can be monitored.[3] However, a study in children showed that dosage based on determination of the GFR results in more consistent carboplatin exposure than dosage based on body-surface area.[6]

1. Calvert AH, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7:** 1748–56.
2. Millward MJ, *et al.* Carboplatin dosing based on measurement of renal function—experience at the Peter MacCallum Cancer Institute. *Aust N Z J Med* 1996; **26:** 372–9.
3. Duffull SB, Robinson BA. Clinical pharmacokinetics and dose optimisation of carboplatin. *Clin Pharmacokinet* 1997; **33:** 161–83.
4. Chatelut E, *et al.* Population pharmacokinetics of carboplatin in children. *Clin Pharmacol Ther* 1996; **59:** 436–43.
5. Chatelut E, *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; **87:** 573–80.
6. Thomas H, *et al.* Prospective validation of renal-function-based carboplatin dosing in children with cancer: a United Kingdom Children's Cancer Study Group Trial. *J Clin Oncol* 2000; **18:** 3614–21.

Administration in renal impairment. The initial dose of carboplatin is usually determined using a formula (see Administration, above). If this approach is not adopted, the UK licensed product information recommends the following doses based on the patient's creatinine clearance (CC):

- CC 40 mL/minute or more: 400 mg/m^2
- CC 20 to 39 mL/minute: 250 mg/m^2

However, in the USA, the licensed information recommends:

- CC 41 to 59 mL/minute: 250 mg/m^2
- CC 16 to 40 mL/minute: 200 mg/m^2

Malignant neoplasms. A preliminary review[1] of carboplatin, concluded that it was active in ovarian cancer (p.670), with similar responses to those seen with cisplatin; its activity in small-cell lung cancer (p.668), seminoma, and squamous cell carcinomas of the head and neck seemed likely to be comparable, whereas results in gastrointestinal and breast cancers, lymphomas and leukaemias, melanoma, mesothelioma, renal carcinoma, and sarcoma were, generally unimpressive. A subsequent review[2] suggested that in testicular cancer, where there was a prospect of cure, cisplatin, which appeared to give better results in some studies should be preferred. However, in ovarian cancer, where treatment was largely palliative, carboplatin had the advantage of being better tolerated. A further review[3] of randomised studies concurred that carboplatin was equivalent to cisplatin in suboptimally debulked ovarian cancer and extensive-stage small-cell lung cancer, and was inferior to cisplatin in testicular cancer. It was also concluded that carboplatin was inferior to cisplatin in head and neck and oesophageal cancers. There was insufficient comparative evidence for other cancers for which cisplatin has a role.

1. Wagstaff AJ, *et al.* Carboplatin: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of cancer. *Drugs* 1989; **37:** 162–90.
2. Anonymous. Cisplatin or carboplatin for ovarian and testicular cancer? *Drug Ther Bull* 1994; **32:** 62–3.
3. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999; **17:** 409–22.

Preparations

BP 2008: Carboplatin Injection;
USP 31: Carboplatin for Injection.

Proprietary Preparations (details are given in Part 3)

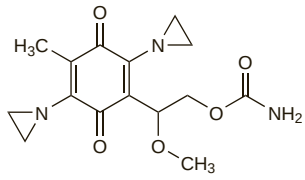
Arg.: Carbokebir; Carboplat; Carboxtie; Omilipis; Paraplatin†; ***Austria:*** Carbosol; Paraplatin; ***Belg.:*** Carbosin; Paraplatin; ***Braz.:*** B-Platin; Biocarbo; Displata†; Evocarb†; Oncocarb†; Oncoplatin; Paraplatin; Platamine; Platicarb†; Tecnocarb; Vancel; ***Canad.:*** Paraplatin; ***Chile:*** Blastocarb†; Oncocarb; Paraplatin; ***Cz.:*** Cycloplatin; Paraplatin†; ***Denm.:*** Paraplatin; ***Fin.:*** Carbosin†; Paraplatin; ***Fr.:*** Paraplatine; ***Ger.:*** Carbo-cell; Carbomedac; Carboplat; Neocarbo; Ribocarbo; ***Gr.:*** Carboplamin; Carbosin; Emorzim; Megaplatin; Paraplatin; ***Hong Kong:*** Paraplatin; ***Hung.:*** Cycloplatin; Paraplatin; ***India:*** Biocarb; Cytocarb; Kemocarb; ***Indon.:*** Carbosin; Paraplatin; ***Irl.:*** Paraplatin; ***Israel:*** Paraplatin†; ***Ital.:*** Paraplatin; ***Malaysia:*** Carbosin; Paraplatin†; ***Mex.:*** Blastocarb; Boplatex; Carboplat; Carbotec; Ifacap; Kemocarb; Novoplat†; Paraplatin; ***Neth.:*** Carbosin; Paraplatin†; ***Norw.:*** Carbosin; Paraplatin; ***NZ:*** Carbosin†; Paraplatin; ***Philipp.:*** Biovinate; Bonaplatin; Carbotinol; Crobextin; Kemocarb; Paraplatin; ***Pol.:*** Cycloplatin; Paraplatin; ***Port.:*** Nealorin; Novoplatinum; Paraplatin; ***Rus.:*** Blastocarb (Бластокарб); Cycloplatin (Циклоплатин); Paraplatin (Параплатин); ***S.Afr.:*** Carbosin; Paraplatin; ***Singapore:*** Paraplatin; ***Spain:*** Ercar†; Nealorin; Paraplatin; Platinwas; ***Swed.:*** Paraplatin; ***Switz.:*** Paraplatin; ***Thai.:*** Blastocarb; Carbosin; Kemocarb; Paraplatin; ***Turk.:*** Carbosin; Paraplatin; Platinwas; ***UK:*** Paraplatin; ***USA:*** Paraplatin†; ***Venez.:*** Bioplatinex; Oplat.

Carboquone *(rINN)*

Carbazilquinone; Carbocuona; Carboquonum; Karbokvon; Karbokvoni. 2,5-Bis(aziridin-1-yl)-3-(2-hydroxy-1-methoxyethyl)-6-methyl-*p*-benzoquinone carbamate.

Карбохон

$C_{15}H_{19}N_3O_5$ = 321.3.
CAS — 24279-91-2.
ATC — L01AC03.
ATC Vet — QL01AC03.



Profile

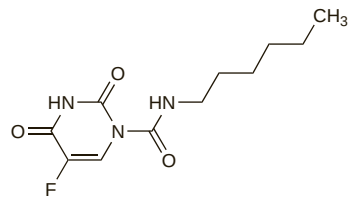
Carboquone is an alkylating agent that has been used in the treatment of a variety of malignant neoplasms including those of the lung, stomach, and ovary; it has also been used in lymphomas and in chronic myeloid leukaemia. It has been given by the intravenous or intra-arterial route, or orally.

Carmofur *(rINN)*

Carmofurum; HCFU; Karmofuuri. 5-Fluoro-*N*-hexyl-3,4-dihydro-2,4-dioxo-1-(2*H*)-pyrimidinecarboxamide; 1-Hexylcarbamoyl-5-fluorouracil.

Кармофур

$C_{11}H_{16}FN_3O_3$ = 257.3.
CAS — 61422-45-5.
ATC — L01BC04.
ATC Vet — QL01BC04.



Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Carmofur is an orally active derivative of fluorouracil (p.722) and has similar actions. It is used in the adjuvant treatment of colorectal cancer, and has been used in breast and ovarian cancers. Carmofur has been associated with the development of neurological disorders including leukoencephalopathy.

◊ References.

1. Yamada T, *et al.* Leukoencephalopathy following treatment with carmofur: a case report and review of the Japanese literature. *Asia Oceania J Obstet Gynaecol* 1989; **15:** 161–8.
2. Sakamoto J, *et al.* An individual patient data meta-analysis of long supported adjuvant chemotherapy with oral carmofur in patients with curatively resected colorectal cancer. *Oncol Rep* 2001; **8:** 697–703.
3. Nakamura T, *et al.* Optimal duration of oral adjuvant chemotherapy with Carmofur in the colorectal cancer patients: the Kansai Carmofur Study Group trial III. *Int J Oncol* 2001; **19:** 291–8.
4. Tominaga T, *et al.* Postoperative chemoendocrine therapy for women with node-positive stage II breast cancer with combined cyclophosphamide, tamoxifen, and 1-hexylcarbamoyl-5-fluorouracil. *Eur J Surg* 2001; **167:** 598–604.
5. Iwagaki H, *et al.* Post-operative adjuvant chemotherapy for colorectal cancer with 5-fluorouracil (5-FU) infusion combined with 1-hexylcarbamoyl-5-fluorouracil (HCFU) oral administration after curative resection. *Anticancer Res* 2001; **21:** 4163–8.
6. Morimoto K, Koh M. Postoperative adjuvant use of carmofur for early breast cancer. *Osaka City Med J* 2003; **49:** 77–83.
7. Tominaga T, *et al.* 1-Hexylcarbamoyl-5-fluorouracil + cyclophosphamide + tamoxifen versus CMF + tamoxifen in women with lymph node-positive breast cancer after primary surgery: a randomized controlled trial. *Oncol Rep* 2004; **12:** 797–803.
8. Sakamoto J, *et al.* An individual patient data meta-analysis of adjuvant therapy with carmofur in patients with curatively resected colon cancer. *Jpn J Clin Oncol* 2005; **35:** 536–44.

Preparations

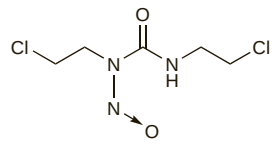
Proprietary Preparations (details are given in Part 3)
Fin.: Mirafur.

Carmustine *(BAN, USAN, rINN)*

BCNU; BiCNU; Carmustina; Carmustinum; Karmustiini; Karmustin; Karmustinas; Karmusztin; NSC-409962; WR-139021. 1,3-Bis(2-chloroethyl)-1-nitrosourea.

Кармустин

$C_5H_9Cl_2N_3O_2$ = 214.0.
CAS — 154-93-8.
ATC — L01AD01.
ATC Vet — QL01AD01.



Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Carmustine). A yellowish, granular powder. Very slightly soluble in water; freely soluble in dehydrated alcohol; very soluble in dichloromethane. It melts at about 31° with decomposition. Store at a temperature of 2° to 8° in airtight containers. Protect from light.

Stability. The manufacturers state that, when reconstituted, resulting carmustine solutions (undiluted or further diluted in sodium chloride 0.9% or glucose 5%) are stable for 8 hours at room temperature, or 24 hours at 2° to 8°, when protected from light. There is some evidence that carmustine interacts with plastic giving sets and containers, and licensed product information recommends the use of polyethylene or glass.

A study has indicated that diluted solutions of carmustine undergo increased degradation in the presence of sodium bicarbonate, with only 73% of the original concentration of carmustine remaining after 90 minutes, much of the loss being in the first 15 minutes.[1]

1. Colvin M, *et al.* Stability of carmustine in the presence of sodium bicarbonate. *Am J Hosp Pharm* 1980; **37:** 677–8.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639. Delayed and cumulative bone-marrow depression is the most frequent and serious adverse effect of intravenous carmustine. Platelets and leucocytes are mainly affected, with platelet nadirs occurring at 4 to 5 weeks after a dose and leucocyte nadirs at 5 to 6 weeks; although thrombocytopenia is usually more severe, leucopenia may also be dose-limiting. Other adverse effects include pulmonary fibrosis (mainly but not exclusively at high cumulative doses—see also Effects on the Lungs, p.638), renal and hepatic damage, and neuroretinitis. Nausea and vomiting, beginning up to 2 hours after a dose, is common but can be reduced by prophylactic antiemetic therapy. Venous irritation may follow intravenous injection and transient hyperpigmentation has been noted after contact of a solution with the skin. Flushing of the skin and suffusion of the conjunctiva may occur on rapid intravenous infusion. Hypotension, tachycardia, chest pain, headache, and hypersensitivity reactions have been reported.

Convulsions, cerebral oedema, and various neurological symptoms have been reported in patients given carmustine-containing polymer implants; abnormalities of wound healing at the site of implantation, and an increased incidence of intracranial infection have also been reported.

As with other alkylating agents, carmustine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the eyes. Ocular toxicity has been reported in patients given carmustine,[1,2] and seems to be more likely when given into the carotid artery,[1,2] although it was also seen with high-dose intravenous therapy. There is some evidence that the alcohol diluent used to prepare carmustine solutions may contribute to the retinopathy.[2]

1. Shingleton BJ, *et al.* Ocular toxicity associated with high-dose carmustine. *Arch Ophthalmol* 1982; **100:** 1766–72.
2. Greenberg HS, *et al.* Intra-arterial BCNU chemotherapy for treatment of malignant gliomas of the central nervous system. *J Neurosurg* 1984; **61:** 423–9.

Effects on the lungs. Studies have found a high incidence of fatal pulmonary fibrosis (see also Effects on the Lungs, p.638) in patients treated with carmustine for gliomas during childhood; patients who were treated before 5 or 6 years of age were more likely to die of pulmonary fibrosis than those treated at a later age.[1,2] However, there are reports of pulmonary toxicity and

upper lobe pulmonary fibrosis occurring in adults given carmustine and high-dose chemotherapy.[3]

1. O'Driscoll BR, *et al.* Late carmustine lung fibrosis: age at treatment may influence severity and survival. *Chest* 1995; **107:** 1355–7.
2. Lohani S, *et al.* 25-year study of lung fibrosis following carmustine therapy for brain tumor in childhood. *Chest* 2004; **126:** 1007.
3. Parish JM, *et al.* Upper lobe pulmonary fibrosis associated with high-dose chemotherapy containing BCNU for bone marrow transplantation. *Mayo Clin Proc* 2003; **78:** 630–4.

Extravasation. For mention of the use of sodium bicarbonate as a specific antidote after carmustine extravasation, see under Treatment of Adverse Effects of Antineoplastics, p.640.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Carmustine should be used with extreme caution in children, who are at particular risk of severe delayed pulmonary toxicity. It should also be used with caution in patients with reduced lung function. Lung function should be monitored before and frequently during therapy. Blood counts should be monitored weekly during therapy, and for at least 6 weeks after the last dose. Renal and hepatic function should also be monitored periodically.

Handling and disposal. Carmustine has been shown to permeate latex, PVC, and rubber gloves, the degree of permeation tending to increase with time,[1-3] up to an equilibrium value.[2] The permeation rate appears not to depend solely on glove thickness and material, and may be different for different gloves made from the same material.[2] The time for initial penetration was reported to vary between 4.7 and 66.0 minutes in one study,[2] and gloves could be chosen accordingly depending on the anticipated length of exposure. Double-gloving, particularly with thicker PVC[1] or ethylmethacrylate[3] gloves, may offer some additional protection.

1. Connor TH, *et al.* Permeability of latex and polyvinyl chloride gloves to carmustine. *Am J Hosp Pharm* 1984; **41:** 676–9.
2. Thomas PH, Fenton-May V. Protection offered by various gloves to carmustine exposure. *Pharm J* 1987; **238:** 775–7.
3. Mellström GA, *et al.* Barrier effect of gloves against cytostatic drugs. *Curr Probl Dermatol* 1996; **25:** 163–9.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Cimetidine. Reductions in white cell counts and platelet counts well below those normally attributed to treatment with carmustine alone were seen in 6 of 8 patients receiving their first course of carmustine and steroids with cimetidine given prophylactically,[1] and in 9 patients in a further study.[2] Cimetidine was also reported to exacerbate the neutropenia and leucopenia in a patient receiving lomustine.[3]

1. Selker RG, *et al.* Bone-marrow depression with cimetidine plus carmustine. *N Engl J Med* 1978; **299:** 834.
2. Volkin RL, *et al.* Potentiation of carmustine-cranial irradiation-induced myelosuppression by cimetidine. *Arch Intern Med* 1982; **142:** 243–5.
3. Hess WA, Kornblith PL. Combination of lomustine and cimetidine in the treatment of a patient with malignant glioblastoma: a case report. *Cancer Treat Rep* 1985; **69:** 733.

Pharmacokinetics

Intravenous carmustine is rapidly metabolised, and no intact drug is detectable after 15 minutes; metabolites have a much longer half-life and are presumed to be responsible for its activity. It is primarily excreted in the urine; some is also excreted as carbon dioxide, via the lungs. Carmustine readily crosses the blood-brain barrier, appearing in CSF in substantial concentrations almost immediately after intravenous injection. Carmustine diffuses from polymer implants into surrounding brain tissue; however, tissue and plasma concentrations after implantation have not been determined.

Uses and Administration

Carmustine is a cell-cycle phase non-specific antineoplastic belonging to the nitrosourea group of compounds, which are considered to function as alkylating agents. It is believed to alkylate DNA and RNA, and may also inhibit enzymatic processes by carbamoylation of amino acids in proteins. Carmustine is used in the treatment of brain tumours, and in combination chemotherapy for multiple myeloma. It may be given as second-line therapy in Hodgkin's disease, non-Hodgkin's lymphoma, and some other malignancies (see below).

Carmustine is licensed for use as a single agent either as a single dose of 150 to 200 mg/m^2 or divided into doses of 75 to 100 mg/m^2 given on 2 successive days. Doses are given by intravenous infusion over 1 to 2 hours in sodium chloride 0.9% or glucose 5%. Lower doses are usually given in combination therapy, except for conditioning before stem-cell transplantation. Doses may be repeated every 6 weeks provided that blood counts have returned to acceptable levels. Subsequent doses must be adjusted according to the haematological response (see also Bone-marrow Depression, p.639).

Polymer implants containing carmustine have been developed for implantation into the brain in the localised treatment of high-grade malignant glioma or recurrent glioblastoma multiforme. Each implant contains 7.7 mg of carmustine: up to 8 such implants are inserted into the cavity left by surgical removal of the tumour.

Amyloidosis. For mention of chemotherapy with epirubicin, cyclophosphamide, and carmustine to suppress amyloidosis after cardiac transplantation, see p.743.

Malignant neoplasms. Carmustine has been used in chemotherapeutic regimens for a number of malignancies. Because of its ability to pass the blood-brain barrier it has been extensively used in malignant neoplasms of the brain (p.660). As an extension of such use, carmustine-releasing wafers have been implanted directly into the brain.[1] In a multicentre study[2] in patients with recurrent malignant glioma, biodegradable poly(carboxyphenoxypropane/sebacic acid)anhydride polymer wafers containing carmustine implanted into the brain after tumour resection produced a median survival of 31 weeks compared with 23 weeks for placebo. A subsequent small cohort study[3] failed to find a clear survival benefit associated with wafer implantation in recurrent glioma, and reported a higher rate of complications including seizures, cerebral oedema, CSF leaks, sepsis, and wound infections. The limitations of this small study were acknowledged by the authors, and a review[4] that included these studies concluded that despite limited data, carmustine wafers do provide some survival benefit. A randomised trial in 240 patients found that treatment with carmustine wafers reduced the risk of death by 28% compared with placebo;[5] this survival advantage was maintained at 1, 2, and 3 years, with statistical significance at 3 years.[6] The adverse effect profile was similar for carmustine and placebo groups,[5] and a retrospective review[7] found carmustine wafers to be well tolerated with a low incidence of surgical complications such as infection. However, it was noted that, in some patients, neurological symptoms developed during an attempted tapering of dexamethasone dosage after carmustine with radiotherapy and that close supervision of patients is warranted. Treatment effects or necrosis can radiographically mimic recurrent tumour in a proportion of patients;[7] implantation of wafers caused morphological changes of the brain immediately adjacent to the implants.[8]

Other conditions in which carmustine has been employed, include malignant melanoma (p.673), Hodgkin's disease (p.655), and multiple myeloma (p.658).

1. Lin SH, Kleinberg LR. Carmustine wafers: localized delivery of chemotherapeutic agents in CNS malignancies. *Expert Rev Anticancer Ther* 2008; **8:** 343–59.
2. Brem H, *et al.* Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 1995; **345:** 1008–12.
3. Subach BR, *et al.* Morbidity and survival after 1,3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. *Neurosurgery* 1999; **45:** 17–23.
4. Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. *Surg Neurol* 2000; **53:** 458–64.
5. Westphal M, *et al.* A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-oncol* 2003; **5:** 79–88.
6. Westphal M, *et al.* Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; **148:** 269–75.
7. Kleinberg LR, *et al.* Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest* 2004; **22:** 1–9.
8. Giese A, *et al.* Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma. *J Neurooncol* 2004; **66:** 351–60.

Mycosis fungoides. Topical application of carmustine has been used successfully[1-5] in early mycosis fungoides (p.657). Erythema and telangiectasia were the most frequent adverse effects.

1. Zackheim HS, *et al.* Topical carmustine (BCNU) for mycosis fungoides and related disorders: a 10-year experience. *J Am Acad Dermatol* 1983; **9:** 363–74.
2. Zackheim HS, *et al.* Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol* 1990; **22:** 802–10.
3. Zackheim HS. Topical carmustine (BCNU) for patch/plaque mycosis fungoides. *Semin Dermatol* 1994; **13:** 202–6.
4. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. *J Am Acad Dermatol* 2000; **42:** 283–5.
5. Zackheim HS. Topical carmustine (BCNU) in the treatment of mycosis fungoides. *Dermatol Ther* 2003; **16:** 299–302.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: BiCNU; ***Austral.:*** BiCNU; Gliadel; ***Austria:*** Carmubris; ***Belg.:*** Nitrumon†; ***Braz.:*** Becenun; ***Canad.:*** BiCNU; ***Chile:*** BiCNU; Gliadel†; ***Cz.:*** BiCNU; ***Fr.:*** BiCNU; Gliadel; ***Ger.:*** Carmubris; ***Gr.:*** Carmubris; Gliadel; Nitrumon†; ***Hong Kong:*** BiCNU; ***Hung.:*** BiCNU; ***Irl.:*** BiCNU; ***Israel:*** BiCNU†; Gliadel; ***Ital.:*** Gliadel; ***Malaysia:*** BiCNU†; Gliadel; ***Mex.:*** BiCNU; ***Neth.:*** Gliadel; ***NZ:*** BiCNU; ***Philipp.:*** BiCNU; ***Port.:*** Gliadel; ***S.Afr.:*** BiCNU; Gliadel; ***Singapore:*** BiCNU; ***Spain:*** Gliadel; ***Turk.:*** Nitrumon; ***UK:*** BiCNU†; Gliadel; ***USA:*** BiCNU; Gliadel.

Cetuximab *(USAN, rINN)*

C-225; Cétuximab; Cetuximabum. Immunoglobulin G1 (human-mouse monoclonal C225 γ1-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 κ-chain, dimer.

Цетуксимаб

CAS — 205923-56-4.

ATC — L01XC06.

ATC Vet — QL01XC06.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Adverse effects associated with cetuximab include skin reactions, asthenia, and gastrointestinal disturbances. Skin reactions present mainly as an acneform rash, and, if severe, require dosage adjustment (see Uses and Administration, below). Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. Mild reactions include chills, fever, and dyspnoea; severe reactions include bronchospasm, urticaria, hypotension, and loss of consciousness, and fatalities have occurred. Premedication with a histamine H_1-antagonist is recommended, and dose adjustment may be necessary (see below). Cardiopulmonary arrest and/or sudden death has been reported in patients treated with cetuximab and radiation therapy, and cetuximab should be given with caution in head and neck cancer patients with coronary artery disease, congestive cardiac failure, or arrhythmias. Hypomagnesaemia can occur; patients should be monitored for this and accompanying hypocalcaemia and hypokalaemia both during, and for up to 8 weeks after stopping, cetuximab therapy. Interstitial lung disease and pneumonitis have been reported rarely.

Effects on the skin, hair, and nails. Acneform follicular rashes have been reported with cetuximab therapy;[1,2] lesions were pustular and papular,[2-4] and commonly occurred on the face, scalp, chest, and upper back.[1-5] It has been suggested that there is a relationship between rash and response to therapy or survival, i.e. that rash might be a surrogate marker of cetuximab activity;[6] doubling the cetuximab dose in patients without severe initial skin reactions is reported to increase their response rate to therapy.[7] A few cases of lengthening eyelash and eyebrow hair[8] and abnormal growth of chest hair[9] have been described. Paronychia has also been reported,[1,5,10] as have intraoral aphthous ulcers.[1]

Treatment with oral isotretinoin 500 micrograms/kg daily has been reported to successfully clear acneform skin lesions in 2 patients; topical therapy with metronidazole 0.75% gel or erythromycin 1% was also used.[11] Prophylactic oral minocycline 100 mg daily, started on the same day as cetuximab and given for 8 weeks, significantly reduced total facial lesion counts in the first 4 weeks when compared with placebo; this difference tapered by the end of 8 weeks of treatment. Topical tazarotene showed no clinical benefit and caused local irritation that forced tazarotene to be stopped in many patients.[12]

Some have suggested that the clinical findings of papulopustular rash, nail and periungual abnormalities, alterations in hair texture and growth, and dry skin and pruritus, constitute a syndrome unique to the epidermal growth factor receptor (EGFR) inhibitors, believed to be due to EGFR inhibition in the epidermis, hair follicle, and nail matrix.[13]