most stable in sodium chloride injection, with a pH of 6.2, and any increase or decrease in pH appeared to affect stability adversely.[1]

1. Poochikian GK, *et al*. Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin Hydrochloride, p.712. Alopecia and cardiotoxicity may be less pronounced than with doxorubicin, and extravasation of aclarubicin causes less local tissue inflammation. Bone-marrow depression is dose-limiting, with platelet counts reaching a nadir 1 to 2 weeks after dosage, while leucopenia is greatest after 2 to 3 weeks; recovery generally occurs within 4 weeks. Myelosuppression may be particularly severe in patients who have received mitomycin or a nitrosourea.

Incidence of adverse effects. An early review[1] noted that a strikingly high incidence of ECG changes had been seen with aclarubicin, but that although acute cardiotoxicity occurred, the chronic cardiomyopathy classically associated with the anthracyclines (see p.713) appeared to be rare. Alopecia was also rare, although gastrointestinal disturbances and mucositis were as common or more common than with doxorubicin.

1. Warrell RP. Aclacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; **12:** 275–82.

Pharmacokinetics

Aclarubicin is rapidly distributed into tissues after intravenous injection. Clearance is triphasic, with a terminal elimination half-life of about 3 hours; the principal active metabolite has a terminal half-life of about 13 hours. Aclarubicin is extensively metabolised and only about 1% of the total dose is eliminated unchanged. It is excreted in urine, chiefly as metabolites; some is also eliminated in bile.

Uses and Administration

Aclarubicin is an anthracycline antibiotic with antineoplastic actions similar to those of the other anthracyclines (see Doxorubicin Hydrochloride, p.714), although it inhibits RNA synthesis more strongly than DNA synthesis. It has been used as the hydrochloride in the treatment of malignant blood disorders, such as acute myeloid leukaemia (p.652). Aclarubicin hydrochloride 104 mg is equivalent to about 100 mg of aclarubicin. The usual initial dose as a single agent has been the equivalent of 175 to 300 mg/m^2 of aclarubicin, divided over 3 to 7 consecutive days, as intravenous infusions over 30 to 60 minutes. Where appropriate and tolerated, maintenance doses of the equivalent of 25 to 100 mg/m^2 may be given as a single infusion every 3 to 4 weeks. The total dose that can be given over the patient's life-time depends upon cardiological status but most patients have not received more than 400 mg/m^2. Dosages may need to be reduced when given as part of a combination regimen.

◊ An early review of studies in patients with relapsed acute myeloid leukaemia confirmed the activity of aclarubicin, with reported complete remission rates of the order of 12 to 24%.[1] Doses varied from 10 to 30 mg/m^2 daily to higher doses of 75 to 120 mg/m^2 for 2 to 4 days; in general a total dose of about 300 mg/m^2 appeared to be necessary to induce remission. Less information was available concerning activity in acute lymphoblastic leukaemia, but response rates were lower than those in acute myeloid leukaemia. Results in the malignant lymphomas were generally disappointing.

Longer-term follow-up has confirmed that remission rates and survival are similar for induction regimens in acute myeloid leukaemia using either aclarubicin or daunorubicin.[2,3]

1. Warrell RP. Aclacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; **12:** 275–82.
2. de Nully Brown P, *et al*. Long-term survival and development of secondary malignancies in patients with acute myeloid leukemia treated with aclarubicin or daunorubicin plus cytosine arabinoside followed by intensive consolidation chemotherapy in a Danish national phase III trial. *Leukemia* 1997; **11:** 37–41.
3. Öberg G, *et al*. Long-term follow-up of patients ≥60 yr old with acute myeloid leukaemia treated with intensive chemotherapy. *Eur J Haematol* 2002; **68:** 376–81.

AE-941

Profile

AE-941 is an angiogenesis inhibitor derived from shark cartilage extract. It has been investigated for the treatment of non-small cell lung cancer and some other neoplasms.

◊ References.

1. Sauder DN, *et al*. Neovastat (AE-941), an inhibitor of angiogenesis: randomized phase I/II clinical trial results in patients with plaque psoriasis. *J Am Acad Dermatol* 2002; **47:** 535–41.
2. Gingras D, *et al*. Neovastat—a novel antiangiogenic drug for cancer therapy. *Anticancer Drugs* 2003; **14:** 91–6.

Alemtuzumab *(BAN, rINN)*

Alemtutsumabi; Alemtuzumabum; Campath-1; Campath-1H. Immunoglobulin G1 (human-rat monoclonal CAMPATH-1H γ1-chain antihuman antigen CD52), disulfide with human-rat monoclonal CAMPATH-1H light chain, dimer.

Алемтузумаб

CAS — 216503-57-0.

ATC — L01XC04.

ATC Vet — QL01XC04.

NOTE. The name FluCam has been used for a regimen of alemtuzumab with fludarabine. Distinguish from Flucam, which is ampiroxicam (p.19).

Adverse Effects, Treatment, and Precautions

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

Alemtuzumab commonly causes bone marrow depression, which may be severe and prolonged; fatalities have occurred. Auto-immune anaemia and auto-immune thrombocytopenia and haemolytic anaemia have been reported less commonly; however, fatalities have been reported. Single doses greater than 30 mg, or cumulative weekly doses greater than 90 mg should not be used, because of the increased incidence of pancytopenia. Complete blood and platelet counts should be measured weekly during alemtuzumab therapy, and more frequently if anaemia, neutropenia, or thrombocytopenia occur. Treatment should be interrupted if severe myelosuppression or evidence of haematological toxicity are seen and stopped permanently if auto-immune anaemia or auto-immune thrombocytopenia develops. Lymphopenia may be profound with alemtuzumab therapy, and opportunistic infections are common, and occasionally life-threatening. Antimicrobial prophylaxis is recommended from the start of therapy until after completion; if serious infection occurs, treatment should be interrupted. Recovery of lymphocyte counts may take 6 months or longer after stopping treatment.

Alemtuzumab commonly causes an acute cytokine release syndrome. The reaction usually includes rigors, fever, nausea and vomiting, hypotension, rash, urticaria, pruritus, shortness of breath, headache, and diarrhoea. Rarer, more serious reactions may include bronchospasm, syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, myocardial infarction, and cardiac arrest. Cardiac adverse effects have been fatal in some instances. These infusion-related reactions are most common at the start of therapy: the dose must be increased gradually when beginning treatment, or if it is interrupted for 7 days or more. Pre-medication with an oral or intravenous corticosteroid, oral antihistamine, and analgesic should also be used, particularly before the first dose, and with dose increases. If acute infusion reactions persist, the infusion time may be extended to 8 hours from the time of reconstitution.

Other adverse effects include fatigue, anorexia, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, chest pain, hypertension, cyanosis, and bradycardia or tachycardia. Localised oedema, stomatitis, mucositis, and abdominal pain have been reported, as have dizziness, paraesthesia, tremor, and taste loss. Confusion, insomnia or somnolence, depression, or anxiety may occur. Electrolyte disturbances include hyponatraemia and hypocalcaemia. Coughing, haemoptysis, sinusitis, bronchitis, and pharyngitis have been reported.

Alemtuzumab is contra-indicated for patients with active systemic infection, or underlying immunodeficiency.

Infection. Reactivation of hepatitis B[1] and CMV[2] has been reported with the use of alemtuzumab. Patients who have been pretreated with purine analogues or those with advanced disease and not responding to alemtuzumab therapy appear to be at highest risk for infectious complications. Recommendations for screening and prophylaxis[3] and guidelines for management[4] have been published. Six infection-related deaths have been reported[5] after previously untreated patients with B-cell chronic lymphocytic leukaemia were treated with fludarabine and rituximab, followed by alemtuzumab. These deaths may have resulted from a prolonged period of immunosuppression due to the sequencing of these drugs without sufficient recovery time. In the EU, alemtuzumab is licensed for use in patients for whom fludarabine combination chemotherapy is not appropriate.

1. Iannitto E, *et al*. Hepatitis B virus reactivation and alemtuzumab therapy. *Eur J Haematol* 2005; **74:** 254–8.
2. Laurenti L, *et al*. Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: incidence and treatment with oral ganciclovir. *Haematologica* 2004; **89:** 1248–52.
3. Thursky KA, *et al*. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. *Br J Haematol* 2006; **132:** 3–12.
4. O'Brien SM, *et al*. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Clin Lymphoma Myeloma* 2006; **7:** 125–30.
5. Bayer, UK; Genzyme, UK. Important safety information: six infection-related deaths reported after treatment with MabCampath (alemtuzumab) following Fludarabine+Rituximab induction in patients with B-Cell Chronic Lymphocytic Leukemia (CLL) (issued 11th February 2008). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014104&RevisionSelectionMethod=Latest (accessed 12/05/08)

Interactions

There are no formal interaction studies with alemtuzumab; however, it is recommended that it should not be given within 3 weeks of other chemotherapy drugs, and that patients should not receive live viral vaccines for at least 12 months after receiving alemtuzumab.

Pharmacokinetics

In patients with B-cell chronic lymphocytic leukaemia, distribution of alemtuzumab is mainly to the extracellular fluid and plasma. Over 12 weeks, clearance has been found to decrease with repeated dosing, with consequent accumulation in plasma, and the rate of elimination to approach zero-order kinetics. The half-life is reported to be 8 hours after a first dose of 30 mg, and 6 days after the last 30 mg dose. Steady-state concentrations are reached after about 6 weeks of therapy.

◊ References.

1. Rebello P, *et al*. Pharmacokinetics of CAMPATH-1H in BMT patients. *Cytotherapy* 2001; **3:** 261–7.
2. Mould DR, *et al*. Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol* 2007; **64:** 278–91.

Uses and Administration

Alemtuzumab is a humanised derivative of campath-1G, a rat monoclonal antibody to the CD52 antigen found on lymphocytes. Alemtuzumab is used in the treatment of B-cell chronic lymphocytic leukaemia (p.653). The dose of alemtuzumab must be increased gradually to avoid infusion-related reactions (see above). Alemtuzumab should be diluted in 100 mL sodium chloride 0.9% or glucose 5%. The initial dose is 3 mg daily, given as an intravenous infusion over 2 hours (it may be increased up to 8 hours in some patients, see above). This dose should be repeated daily until it is tolerated; the dose should then be increased to 10 mg daily. When this dose is tolerated, the maintenance dose of 30 mg can be started; this dose escalation usually takes 3 to 7 days. A maximum maintenance dose of 30 mg given three times weekly on alternate days can then be used for up to 12 weeks. The dose should be modified according to haematological toxicity.

Alemtuzumab is under investigation for induction therapy in transplantation (see Organ and Tissue Transplantation, p.1810, *et seq*). It is also under investigation for the treatment of multiple sclerosis.

◊ References.

1. Keating MJ, *et al*. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood* 2002; **99:** 3554–61.
2. Osterborg A, *et al*. Clinical effects of alemtuzumab (Campath-1H) in B-cell chronic lymphocytic leukemia. *Med Oncol* 2002; **19** (suppl): S21–S26.
3. Dearden CE, *et al*. Alemtuzumab in T-cell malignancies. *Med Oncol* 2002; **19** (suppl): S27–S32.
4. Kennedy B, Hillmen P. Immunological effects and safe administration of alemtuzumab (MabCampath) in advanced B-cLL. *Med Oncol* 2002; **19** (suppl): S49–S55.
5. Rai KR, *et al*. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. *J Clin Oncol* 2002; **20:** 3891–7.