but systemic chemotherapy is the treatment of choice.[1-3,5,6] The main combination regimens use a vinca alkaloid and bleomycin, with or without doxorubicin.[2,3] Liposomal formulations of doxorubicin and daunorubicin have produced response rates of 40-85%, and may be less toxic than conventional chemotherapy;[2,3,8] it has been suggested that a liposomal anthracycline is the drug of choice in extensive disease.[1,2,5-7] Paclitaxel is also used as a single agent in advanced disease.[2,3,7,8] However, although highly effective, doses may need to be reduced if given to patients taking HAART because of the risk of drug interactions.[5,7] Although data are limited, docetaxel may be a reasonable alternative.[7] Some response has also been reported for oral etoposide.[1]

Control of Kaposi's sarcoma has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but tumour regression ceased and regrowth occurred when dosage was reduced or withdrawn.[9] Further reports of intralesional or systemic use have included partial remissions and disease stabilisation, as well as no effect or disease progression. The reasons for these contradictory results are unclear, but they may be due to variability in chorionic gonadotrophin preparations, which contain a mixture of biological contaminants. A cytotoxic ribonuclease and the degradation product of the β-hCG subunit have been proposed as active contaminants against Kaposi's sarcoma, but other contaminants may stimulate the tumour.[10] Other lines of investigation include the use of sulfated polysaccharide peptidoglycans, imatinib, other inhibitors of angiogenesis including thalidomide, and the retinoids.[1,5-8]

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SOFT-TISSUE SARCOMA. Soft-tissue sarcomas are a varied group of malignant tumours that originate from mesenchymal stem cells residing in muscle, fat, or connective tissue,[1,2] and whose subtypes vary in terms of prognosis and response to different treatments.[3] The majority of soft-tissue sarcomas occur in the limb or limb girdle; some occur within the abdomen (retroperitoneal), in the head or neck, or in the gastrointestinal tract.[4,5] Patients have a 5-year survival rate of about 50 to 60%;[4] survival in those with extremity sarcomas is better than that in patients with retroperitoneal sarcomas.[2] Tumours often metastasise to the lung; those arising in the abdomen metastasise to the liver and peritoneum.[4]

Rhabdomyosarcoma is the commonest soft-tissue sarcoma in childhood, and is thought to arise from progenitor cells for skeletal muscle. The most frequent sites are the head and neck, genito-urinary tract, and extremities. Some genetic disorders are associated with rhabdomyosarcoma.[6,7] All patients are presumed to have micrometastatic disease at diagnosis; histologically the most common types are embryonal, which occurs at an earlier age, and alveolar, which is more common in adolescents.[7]

The **gastrointestinal stromal tumours** (GISTs) are soft-tissue sarcomas arising in the gastrointestinal tract, most commonly in the stomach and small bowel.[4,8,9] Symptoms may include abdominal pain, anorexia, weight loss, haemorrhage, changes in bowel movements, bowel obstruction, or perforation. Patients with liver metastases may have oedema of the lower extremity, ascites, or jaundice.[10] Spread to the lungs and other locations is seen only in advanced cases.[4]

Surgery is the primary **therapy** for soft-tissue sarcomas,[1,2,4,8] and may be curative for localised disease.[5,11] Radiotherapy, as external-beam therapy or brachytherapy, may be given with surgery, or alone if surgery is inappropriate or declined by the patient.[5] Radiation may be given pre-operatively, during surgery, or postoperatively;[1] optimal timing is unclear.[5,8] Similar rates of local control and progression-free survival have been reported for pre- and postoperative radiotherapy, although pre-operative treatment has been associated with a greater incidence of wound complications, especially in lower extremity tumours.[4] Postoperative radiation can cause acute and delayed bowel toxicity in those with retroperitoneal tumours, and significant toxicity has occurred with the use of brachytherapy, especially when used in the upper abdomen.[2]

Surgery and/or radiotherapy may be combined with chemotherapy. Pre-operative chemotherapy may allow for more efficient resection of the tumour.[1,8] The use of postoperative chemotherapy is controversial,[5,8] except for some tumours such as extraosseous Ewing's sarcoma or rhabdomyosarcoma. For these tumours, combinations of vincristine, dactinomycin, doxorubicin, cyclophosphamide, ifosfamide, or etoposide form the basis of most regimens.[5-8]

For those with unresectable or metastatic disease, chemotherapy may be palliative; ifosfamide and doxorubicin are routinely used in this setting.[5] These may be used as single agents or in combination; other acceptable single agent choices are dacarbazine, gemcitabine, or liposomal doxorubicin.[4] Data support the use of adjuvant doxorubicin-based chemotherapy to improve disease-free survival;[12] however, overall survival is not improved. For palliative treatment in advanced soft-tissue sarcoma, a systematic review[13] concluded that combination chemotherapy did not significantly increase survival rates compared with single-agent doxorubicin. A retrospective analysis[14] found that, in patients with high-risk disease, clinical benefits of doxorubicin-based chemotherapy were not sustained beyond 1 year. There is no consensus on the best second-line chemotherapy regimen for patients with metastatic disease refractory to doxorubicin- or ifosfamide-based regimens.[2,3] Dose-intensified combination regimens, with colony-stimulating factor support, have been investigated as adjuvant therapy[15] and in advanced disease;[16] although both these studies found a delay in disease progression, a beneficial effect on overall survival was only found in the former. Intensive combination chemotherapy benefited a subgroup of children with metastatic rhabdomyosarcoma and fewer than 2 unfavourable risk factors, in terms of event-free survival and overall survival. However, most patients have more than 2 risk factors; these patients should be considered for novel first-line therapies. No evidence was found for improved outcome after consolidation therapy with high-dose melphalan and autologous bone marrow or peripheral-blood stem cell rescue.[17] Response to topotecan has been reported in a study of metastatic rhabdomyosarcoma,[18] and trabectedin has shown some activity in advanced soft-tissue sarcomas.[3,5] Tasonermin and melphalan can be used together for isolated limb perfusion of unresectable soft-tissue sarcomas, but severe toxicity may limit use of this regimen. Potential salvage therapy options after failure of first-line therapy include paclitaxel, docetaxel, gemcitabine, trofosfamide, temozolomide, and various combinations thereof.[3]

Surgery is used for localised, resectable disease arising in the gastrointestinal tract, although this does not routinely cure GISTs; median time to recurrence after resection is about 2 years. Adjuvant imatinib is under investigation in this setting. Imatinib produces durable clinical benefit and objective responses in most patients with GISTS, including those with metastatic or unresectable disease. If the tumour responds to imatinib, surgical resection may be indicated. In patients with imatinib-resistant GIST, or who experience life-threatening adverse effects such as hepatotoxicity and fluid retention with imatinib, sunitinib may be considered.[4,8,9,19]

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Aclarubicin *(BAN, USAN, rINN)*

Aclacinomycin A; Aclarubicina; Aclarubicine; Aclarubicinum; Aklarubicin; Aklarubisiini; Aklarubisin; NSC-208734. Methyl (1*R*,2*R*,4*S*)-4-(*O*-{2,6-dideoxy-4-*O*-[(2*R*,6*S*)-tetrahydro-6-methyl-5-oxopyran-2-yl]-α-L-*lyxo*-hexopyranosyl}-(1→4)-2,3,6-trideoxy-3-dimethylamino-L-*lyxo*-hexopyranosyloxy)-2-ethyl-1,2,3,4,6,11-hexahydro-2,5,7-trihydroxy-6,11-dioxonaphthacene-1-carboxylate.

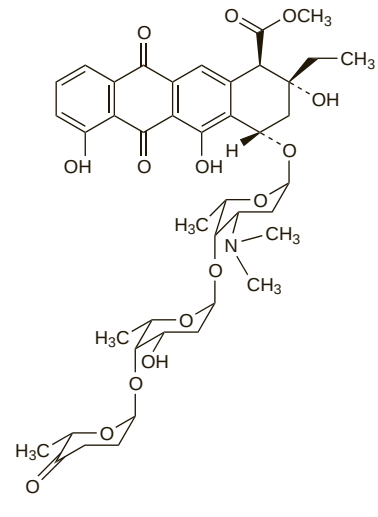
Акларубицин

$C_{42}H_{53}NO_{15}$ = 811.9.

CAS — 57576-44-0.

ATC — L01DB04.

ATC Vet — QL01DB04.



Description. Aclarubicin is an anthracycline antineoplastic antibiotic isolated from *Streptomyces galilaeus*.

Aclarubicin Hydrochloride *(BANM, rINNM)*

Aclarubicine, Chlorhydrate d'; Aclarubicini Hydrochloridum; Hidrocloruro de aclarubicina.

Акларубицина Гидрохлорид

$C_{42}H_{53}NO_{15}$,HCl = 848.3.

CAS — 75443-99-1.

ATC — L01DB04.

ATC Vet — QL01DB04.

Pharmacopoeias. In *Jpn*.

Stability. In a study of the stability of anthracycline antineoplastic agents in 4 infusion fluids—glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid—stability appeared to be partly related to pH; aclarubicin was

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]

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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.
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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.

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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.

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3. Dearden CE, *et al*. Alemtuzumab in T-cell malignancies. *Med Oncol* 2002; **19** (suppl): S27–S32.
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