of vascular injury was unrelated to cardiac dysfunction. Trastuzumab therapy was stopped permanently and her symptoms gradually resolved over the course of a year.[1]

1. Pansegrau GK, *et al.* Trastuzumab-associated peripheral vascular toxicity. *J Clin Oncol* 2007; **25:** 1438–40.

Pregnancy. A 28-year-old woman who had been given trastuzumab 6 mg/kg every 3 weeks was found to be pregnant after 5 months of therapy. Trastuzumab was stopped at about 20 weeks of gestation. Ultrasound study of the fetus at 23 weeks indicated no amniotic fluid. On observation, the anhydramnios slowly resolved. No further complications occurred and a healthy female infant was induced at 37+ weeks; amniotic fluid was clear at delivery.[1] Similarly, 2 cycles of trastuzumab and paclitaxel were given to a 38-year-old pregnant woman between 26 and 32 weeks of gestation: fetal abdominal circumference stopped increasing and the volume of amniotic fluid decreased to almost total anhydramnios. There was also evidence of fetal renal failure. Fetal lung maturation was induced and a caesarean section done at about 32 weeks of gestation. The infant showed signs of bacterial sepsis with hypotension, transient renal failure, and respiratory failure necessitating mechanical ventilation. After antibacterial therapy, blood pressure normalised, ventilation was ended, and diuresis was deemed adequate. He was discharged at age 6 weeks in healthy condition and development at 12 weeks of age was deemed to be normal.[2] In another report, a 30-year-old patient conceived 3 days after her second cycle of trastuzumab; no further therapy was given. Her pregnancy went successfully to term and a healthy female was born with no sequelae.[3] Low amniotic fluid volume was seen in another case of trastuzumab use during pregnancy; at 5 years of age, the child was reported to have normal growth and development.[4]

1. Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. *Obstet Gynecol* 2005; **105:** 642–3.
2. Bader AA, *et al.* Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 2007; **8:** 79–81.
3. Waterston AM, Graham J. Effect of adjuvant trastuzumab on pregnancy. *J Clin Oncol* 2006; **24:** 321–2.
4. Pant S, *et al.* Treatment of breast cancer with trastuzumab during pregnancy. *J Clin Oncol* 2008; **26:** 1567–9.

Interactions

For reports of trastuzumab enhancing the effect of warfarin, see p.1429.

Pharmacokinetics

The half-life of trastuzumab varies considerably: it has been reported to be 1.7 days after a 10-mg dose, 12 days after a 500-mg dose, and 5.8 days after the recommended dose (4 mg/kg followed by 2 mg/kg weekly); 28.5 days has also been reported after the recommended dose. Detectable concentrations of the cell surface protein of the HER2 receptor (shed antigen) have been found in patients' serum; those patients with higher baseline values for shed antigen had lower serum trough concentrations of trastuzumab, although target trastuzumab concentrations were still achieved after weekly dosing, and no relationship to clinical response was observed.

Uses and Administration

Trastuzumab is a humanised monoclonal antibody directed against a cell surface protein produced by the human epidermal growth factor receptor 2 (HER2) gene. HER2 protein is overexpressed in about one-third of all breast cancers. Trastuzumab is used in the treatment of breast cancer (p.661) with such characteristics.

The recommended dose in **metastatic** breast cancer, alone, with an aromatase inhibitor, or followed by a taxane, is 4 mg/kg initially, by intravenous infusion in 250 mL of sodium chloride 0.9% over 90 minutes. This may be followed by 2 mg/kg over 30 minutes at weekly intervals.

Trastuzumab is also given in **early** breast cancer after surgery, chemotherapy, and radiotherapy. There are 2 recommended schedules, with trastuzumab given either weekly or every 3 weeks.

- The recommended dose for the 3-weekly schedule is 8 mg/kg initially, by intravenous infusion in 250 mL sodium chloride 0.9% over 90 minutes. This may be followed by 6 mg/kg at 3-weekly intervals. Treatment is continued for 1 year or until disease recurrence.

  If the patient misses a dose of trastuzumab by 1 week or less, then the usual dose of 6 mg/kg should be given as soon as possible, without waiting until the next planned cycle. Subsequent cycles are then given according to the previous schedule.

  If the dose is missed by more than 1 week, a re-loading dose of trastuzumab 8 mg/kg should be given, and subsequent maintenance doses of 6 mg/kg should then be given every 3 weeks thereafter.
- In the weekly schedule, trastuzumab is given with paclitaxel after 4 cycles of the AC regimen (doxorubicin and cyclophosphamide). It is given at an initial loading dose of 4 mg/kg followed by 2 mg/kg weekly thereafter for 1 year; paclitaxel is given either weekly or 3-weekly for a total of 12 weeks.

HER2 may also be overexpressed in other epithelial cancers, and trastuzumab is under investigation for use in non-small cell lung cancer, pancreatic, prostate, and ovarian malignancies.

◊ References.

1. Spigel DR, Burstein HJ. Trastuzumab regimens for HER2-over-expressing metastatic breast cancer. *Clin Breast Cancer* 2003; **4:** 329–37.
2. Ferrone M, Motl SE. Trastuzumab for the treatment of non-small-cell lung cancer. *Ann Pharmacother* 2003; **37:** 1904–8.
3. Langer CJ, *et al.* Trastuzumab in the treatment of advanced non—small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group Study 2598. *J Clin Oncol* 2004; **22:** 1180–7.
4. Tripathy D, *et al.* Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol* 2004; **22:** 1063–70.
5. Papazisis KT, *et al.* Safety and efficacy of the combination of trastuzumab with docetaxel for HER2-positive women with advanced breast cancer: a review of the existing clinical trials and results of the expanded access programme in the UK. *Int J Clin Pract* 2004; **58:** 581–6.
6. Jones RL, Smith IE. Efficacy and safety of trastuzumab. *Expert Opin Drug Saf* 2004; **3:** 317–27.
7. Piccart-Gebhart MJ, *et al.* HERA Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1659–72.
8. Romond EH, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1673–84.
9. Kabe KL, Kolesar JM. Role of trastuzumab in adjuvant therapy for locally invasive breast cancer. *Am J Health-Syst Pharm* 2006; **63:** 527–33.
10. Plosker GL, Keam SJ. Trastuzumab: a review of its use in the management of HER2-positive metastatic and early-stage breast cancer. *Drugs* 2006; **66:** 449–75.
11. Smith I, *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; **369:** 29–36.
12. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med* 2007; **357:** 39–51.
13. Orman JS, Perry CM. Trastuzumab: in HER2 and hormone receptor co-positive metastatic breast cancer. *Drugs* 2007; **67:** 2781–9.

Preparations

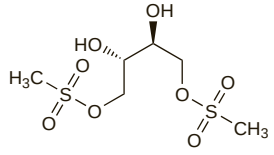
Proprietary Preparations (details are given in Part 3)
Arg.: Herceptin; ***Austral.:*** Herceptin; ***Belg.:*** Herceptin; ***Braz.:*** Herceptin; ***Canad.:*** Herceptin; ***Chile:*** Herceptin; ***Cz.:*** Herceptin; ***Denm.:*** Herceptin; ***Fin.:*** Herceptin; ***Fr.:*** Herceptin; ***Ger.:*** Herceptin; ***Gr.:*** Herceptin; ***Hong Kong:*** Herceptin; ***Hung.:*** Herceptin; ***Indon.:*** Herceptin; ***Irl.:*** Herceptin; ***Israel:*** Herceptin; ***Ital.:*** Herceptin; ***Jpn:*** Herceptin; ***Malaysia:*** Herceptin; ***Mex.:*** Herceptin; ***Neth.:*** Herceptin; ***Norw.:*** Herceptin; ***NZ:*** Herceptin; ***Philipp.:*** Herceptin; ***Pol.:*** Herceptin; ***Port.:*** Herceptin; ***Rus.:*** Herceptin (Герцептин); ***S.Afr.:*** Herceptin; ***Singapore:*** Herceptin; ***Spain:*** Herceptin; ***Swed.:*** Herceptin; ***Switz.:*** Herceptin; ***Thai.:*** Herceptin; ***Turk.:*** Herceptin; ***UK:*** Herceptin; ***USA:*** Herceptin; ***Venez.:*** Herceptin.

Treosulfan *(BAN, rINN)*

Dihydroxybusulphan; NSC-39069; Treosulfaani; Tréosulfan; Treosulfano; Treosulfanum. L-Threitol 1,4-dimethanesulphonate.

Треосульфан

$C_6H_{14}O_8S_2$ = 278.3.
CAS — 299-75-2.
ATC — L01AB02.
ATC Vet — QL01AB02.



Profile

Treosulfan is an antineoplastic agent related to busulfan (p.690), which is reported to act by alkylation after conversion *in vivo* to epoxide compounds. It is used palliatively or as an adjunct to surgery mainly in the treatment of ovarian cancer (p.670).

Treosulfan 1 g daily is licensed for oral use in 4 divided doses for 2 or 4 weeks followed by the same period without treatment. Alternatively 1.5 g daily in 3 divided doses may be given for 1 week, followed by 3 weeks without therapy. The cycle is then repeated, the dose being adjusted if necessary according to the effect on bone marrow. Doses of 3 to 8 g/m^2 may instead be given intravenously every 1 to 3 weeks. Doses larger than 3 g/m^2 should be given by infusion at a rate of 3 g/m^2 every 5 to 10 minutes. Doses up to 1.5 g/m^2 have been given intraperitoneally. Lower doses should be used if treatment with other antineoplastic drugs or radiotherapy is being given.

Regular blood counts should be made and treatment should be interrupted if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p.639). Because bone-marrow depression may be cumulative the interval between blood counts should be reduced after the second course of treatment with treosulfan.

Preparations

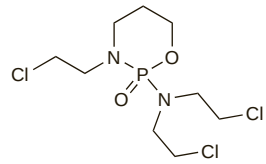
Proprietary Preparations (details are given in Part 3)
Ger.: Ovastat.

Trofosfamide *(rINN)*

A-4828; NSC-109723; Trilophosphamide; Trofosfamid; Trofosfamida; Trofosfamidi; Trofosfamidum; Trophosphamide; Z-4828. 3-(2-Chloroethyl)-2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,-2-oxazaphosphorine-2-oxide.

Трофосфамид

$C_9H_{18}Cl_3N_2O_2P$ = 323.6.
CAS — 22089-22-1.
ATC — L01AA07.
ATC Vet — QL01AA07.



Profile

Trofosfamide is a derivative of cyclophosphamide (p.702) and has the same general properties. It is used in the treatment of malignant disorders in usual initial oral doses of 300 to 400 mg daily. Doses of 50 to 150 mg daily have been given for maintenance therapy.

Uses. References[1-10] to the use of trofosfamide, including its investigational use with pioglitazone and rofecoxib as antiangiogenic therapy.[4,5,7]

1. Gunsilius E, *et al.* Palliative chemotherapy in pretreated patients with advanced cancer: oral trofosfamide is effective in ovarian carcinoma. *Cancer Invest* 2001; **19:** 808–11.
2. Reichardt P, *et al.* Oral trofosfamide: an active and well-tolerated maintenance therapy for adult patients with advanced bone and soft tissue sarcomas: results of a retrospective analysis. *Onkologie* 2002; **25:** 541–6.
3. Andersson PO, *et al.* Trofosfamide as salvage therapy for anaplastic large cell lymphoma relapsing after high-dose chemotherapy. *Leuk Lymphoma* 2002; **43:** 2351–3.
4. Vogt T, *et al.* Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors. *Cancer* 2003; **98:** 2251–6.
5. Reichle A, *et al.* Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. *Cancer* 2004; **101:** 2247–56.
6. Latz D, *et al.* Trofosfamide in the palliative treatment of cancer: a review of the literature. *Onkologie* 2004; **27:** 572–6.
7. Coras B, *et al.* Antiangiogenic therapy with pioglitazone, rofecoxib, and trofosfamide in a patient with endemic kaposi sarcoma. *Arch Dermatol* 2004; **140:** 1504–7.
8. Jahnke K, *et al.* Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma. *Ann Oncol* 2005; **16:** 1974–8.
9. Salminen EK, *et al.* Palliative chemotherapy with trofosfamide in advanced prostate cancer. *Anticancer Res* 2006; **26:** 539–42.
10. Görn M, *et al.* A pilot study of docetaxel and trofosfamide as second-line 'metronomic' chemotherapy in the treatment of metastatic non-small cell lung cancer (NSCLC). *Onkologie* 2008; **31:** 185–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ixoten; ***Ger.:*** Ixoten; ***Spain:*** Genoxal Trofosfamida.

Tumour Necrosis Factor

Factor de necrosis tumoral; TNF.

Tasonermin *(BAN, rINN)*

Tasonermiini; Tasonermina; Tasonermine; Tasonerminum; TNFα-1a.

Тазонермин

$C_{778}H_{1225}N_{215}O_{231}S_2$ = 17350.5.
CAS — 94948-59-1.
ATC — L03AX11.
ATC Vet — QL03AX11.