# Continuous infusion of doxorubicin, epirubicin and mitoxantrone in cancer chemotherapy

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## SUMMARY.

Most types of metastatic solid tumors cannot be cured by the available chemotherapeutic agents. Although this failure is often a result of intrinsic or acquired drug resistance, ineffective drug dosage or scheduling may contribute to treatment inefficacy. The therapeutic index of drugs may be improved by modifying the delivery schedule, such as expanding the infusion time, in order to increase the exposure of metabolically active tumor cells to the drug and simultaneously decrease toxicicty by avoiding high peaklevels of the drug. The recent development of reliable portable pumps suitable for continuous drug administration, and safe long-term venous access catheters has made the infusion of cytostatic agents feasible over periods of several weeks.

In chapter 1 a review is given of continuous infusion regimens with doxorubicin (adriamycin), and our own studies with continuous infusion of epirubicin and mitoxantrone.

In chapter 2 adriamycin and mitoxantrone accumulation are studied in a human small cell lung carcinoma cell line and in the adriamycin resistant subline lacking cross resistance to mitoxantrone. An energy dependent efflux pump is present for adriamycin in the resistant cell line. No pleiotropic drug resistant genotype and phenotype could be detected in this cell line. An energy dependent efflux pump can be present in resistant cells without the pleiotropic drug resistance genotype, and can lead to lower cellular drug concentrations. Lower cellular drug concentrations do not necessarily lead to less cytotoxicity, as seen for mitoxantrone in this study. Resistance to adriamycin should not rule out the use of mitoxantrone, especially in cases not showing pleitropic drug resistance characteristics.

In chapter 3 a phase I and pharmacokinetic study with 21 days continuous infusion of epirubicin is described. A dose of 6 mg/m$^2$/day for 3 weeks was found to be the optimal dose for evaluation of antitumor efficacy in phase II studies. Pharmacokinetic studies were performed by high performance liquid chromatography with fluorometric detection. Plasma steady state was reached after 57 hours of infusion. During steady state there was a linear relationship between epirubicin dose administered and epirubicin level in plasma, and in leucocytes. The area under the curve in leucocytes was higher with continuous infusion of 6 mg/m$^2$/day for 21 days compared with an equal myelotoxic dose of 80 mg/m$^2$ administered as bolus injection. This method of continuous infusion of epirubicin may be a way to increase intracellular drug uptake as expressed by intracellular area under the curve.

In chapter 4 a phase II study with continuous infusion of epirubicin in a dose of 6 mg/m$^2$/day during 21 days repeated every six weeks in patients with advanced metastatic colorectal cancer is described. Fourteen patients were treated with a total of 32 cycles. There were no complete or partial remissions. Stable disease was observed in eleven patients, with a median duration of 12 weeks. Compared to phase II studies with bolus injection of epirubicin every 3 weeks, less myelotoxicity was seen with continuous infusion. We conclude that epirubicin given in a continuous infusion schedule is

well tolerated and causes minimal toxicity, but cannot be recommended for the treatment of patients with metastatic colorectal cancer.

In chapter 5 an update of the preliminary results of a phase II study with continuous infusion of epirubicin in patients with advanced gastric cancer is given. A dose of 6 mg/m$^2$/day during 21 days was administerd and courses were repeated every six weeks. In 18 evaluable patients who received a total of 43 courses two complete responses and one partial response were observed. One patient had a minor response and 10 patients had stable disease with a median duration of 12 weeks. Treatment was very well tolerated and toxicity was limited. Two patients developed a subclavian vein thrombosis due to the totally implantable catheter. We conclude that continuous infusion of epirubicin might be an interesting treatment schedule in patients with advanced gastric cancer. Final assessment of the remission rate must await additional patient data.

In chapter 6 a phase I and pharmacokinetic study with 21 days continuous infusion of mitoxantrone, an anthracenedione with structural similarities to doxorubicin (adriamycin), is described. The maximum tolerated dose for a 21 day continuous infusion schedule was determined in this study, and pharmacokinetic studies were performed in plasma and leukocytes. A maximal tolerated dose of 1.1 mg/m$^2$/day for 21 days continuous infusion was found and recommended for evaluation of antitumor efficacy in phase II studies. Similar to continuous infusion with epirubicin a linear relationship was found between mitoxantrone dose administered and mitoxantrone level in plasma. Steady state in plasma was reached after 35 hours. Mitoxantrone level in leukocytes did still increase significantly during the infusion period, and did not reach steady state. The area under the curve in leukocytes was higher with continuous infusion of 1.1 mg/m$^2$/day for 21 days compared to a bolus injection of 12 mg/m$^2$. Mitoxantrone could be detected in plasma for at least 5 days after the end of the infusion and in leukocytes for at least 14 days after the end of the infusion. Like continuous infusion with epirubicin, continuous infusion of mitoxantrone may be a way to increase intracellular drug uptake as expressed by the intracellular area under the curve.

In chapter 7 an evaluation of a totally implanted venous access port and portable pump in a continuous infusion chemotherapy schedule on an outpatient basis in the first 50 patients is given. The complication rate was low. Subclavian vein thrombosis was seen in one patient, and one patient developed pulmonary embolism. Needle dislocation was observed in two patients. No septicemia was seen. Pump functioning was efficient and mechanical malfunction did not occur. We conclude that a totally implanted venous access port and portable pump are a safe and reliable route of adminstration for cytostatic drugs on an outpatient basis.

In chapter 8 the patient education program for a continuous infusion regimen on an outpatient basis is described. The policies and procedures for the use of the pump, the mixing of the cytostatic drug, and an educational program for patients and their relatives are shown in this chapter.

## CONCLUSION.

This thesis describes some clinical and pharmacokinetic studies with continuous infusion of doxorubicin, epirubicin and mitoxantrone. Continuous infusion has advantages compared to bolus injection therapy. Toxicity, especially myelotoxicity, nausea and vomiting, is decreased with continuous infusion, although the use of a totally implantable venous access port and a portable pump for continuous drug administration may lead to additional complications. Due to the phase I and II character of the studies it is difficult to draw definite conclusions on the efficacy of continuous infusion of doxorubicin, epirubicin and mitoxantrone. Pharmacokinetic studies do show a significant increase in intracellular drug uptake as expressed by intracellular area under the curve with continuous infusion, compared to the intracellular drug uptake after an equimyelotoxic bolus injection. This might lead to a higher tumor response rate with continuous infusion. Further well-controlled comparitive trials are necessary to investigate the role of continuous infusion therapy in cancer treatment. For the patients continuous infusion of cytostatic agents on an outpatient basis is a more attractive treatment schedule compared to a bolus infusion schedule, for which admission to a hospital is often required and which mostly leads to more severe toxicity. In our studies with continuous infusion patients were generally very positive in their reaction on how they experienced treatment with continuous infusion. The fact that they were self-supporting and responsible for their own treatment was a positive experience for most patients and their relatives. In further studies with continuous infusion of cytostatic agents it will be interesting to perform an objective quality of life study in these patients.