Clinical course of haemodialysis patients with malignancies and dose-adjusted chemotherapy

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Abstract

Background. Chemotherapy is not given routinely to patients with malignancies receiving chronic haemodialysis because evidence of a clear benefit is still lacking and severe side effects are feared. The aim of our retrospective study was to analyse the methods of dose adjustment and the clinical course of chronic haemodialysis patients with malignancies treated by chemotherapy.

Methods. Between 1985 and 2001, a total of 48 cycles of 21 chemotherapy protocols were administered to 16 dialysis patients with nine haemoblastic and seven solid malignancies. We compared the dose actually administered with that theoretically derived from the proportional dose reduction rule of Dettli and the rule of Giusti and Hayton, using published pharmacokinetic parameters.

Results. Kaplan–Meier estimates of median survival time were 30 months in patients with haemoblastic malignancies and 10 months for patients with solid malignancies. Eleven chemotherapies were administered in standard dosages and 10 chemotherapies in reduced dosages (39–80% of the regular dose); in all therapies, however, the dose was significantly higher than proposed by the Dettli rule ($P < 0.01$).

Conclusion. Chemotherapy in patients with haemodialysis is feasible. Individual dose adjustment should be performed on the basis of pharmacokinetic data and the general condition of the patient, but it is still a matter of expert judgement, as there is no formal evidence available.

Keywords: chemotherapy; dose adjustment; haemodialysis; malignancies; nephropharmacology; pharmacokinetics

Introduction

Patients with end-stage renal disease have a high incidence of malignancies, and the age of patients on haemodialysis has increased in recent years [1–3]. Thus, the number of haemodialysis patients with malignancies eligible for chemotherapy has increased. In chemotherapy treatment protocols, however, patients with end-stage renal disease and long-term haemodialysis commonly were excluded, because drug elimination and metabolism are unknown, and uraemic immunodeficiency affects the clinical course of these patients [4].

Pharmacokinetic dose adjustment based on blood concentrations was performed for cisplatin/etopside in haemodialysis patients with lung cancer [5], and for 5-fluorouracil (5-FU)/cisplatin in haemodialysis patients with oesophageal cancer [6]. Pharmacokinetic and dynamic dose adjustment has been described for carboplatin with regard to the desired platelet count and creatinine clearance in patients with impaired renal elimination [7,8]. In most cases, serum drug levels are not available, and the pharmacokinetic rules of Dettli [9], and Giusti and Hayton [10] were applied to the dose adjustment of cytotoxic drugs as, for example, for antibiotics.

The aim of our retrospective study was to evaluate the clinical course in patients on haemodialysis with malignancies treated with chemotherapy, and to compare the individual dose adjustment with the models of Dettli, and Giusti and Hayton.

Patients and methods

Patients

All patients on haemodialysis with malignancies treated with chemotherapy at the University Hospital Ulm between 1985 and 2001 were recorded in our retrospective analysis ($n = 41$).
Chemotherapy was administered in the haematology or gastroenterology clinic in consensus with a nephrology consultant. Haemodialysis was performed in our dialysis unit three times per week. Routine clinical and laboratory parameters were recorded.

Inclusion criteria for retrospective analysis were: (i) chronic haemodialysis [end-stage renal disease, glomerular filtration rate (GFR) <10 ml/min, urine output <500 ml per day] before the beginning of chemotherapy; (ii) sufficient availability of data for >4 weeks to evaluate the clinical course during and after chemotherapy; and (iii) the diagnosis of the malignancy must have been confirmed by histopathological findings. Exclusion criteria were: (i) dose reduction due to cardiomyopathy, neuropathy or hepatic insufficiency; (ii) acute dialysis with presumed recovery of renal function; and (iii) a Karnofsky index <40%. Twenty-two of the recorded 41 patients had acute renal failure on chemotherapy and were excluded from our study. In addition, two patients with dose adjustment were excluded due to hepatic dysfunction and one patient because of insufficient availability of data for evaluation.

Our retrospective analysis was approved by the local ethics committee at the University of Ulm. All patients were informed about the side effects of the therapy, and written informed consent was obtained from all patients before therapy.

Data and procedures

Patients’ records were evaluated for laboratory and routine clinical parameters before and during chemotherapy. Severe infections during leukopenia after chemotherapy (white blood cell count <1000 x 10^6/l) were interpreted as therapy-associated adverse events. Study end-points were death either from tumour progression, infection or other causes, or the end of our observation period, December 2001.

Chemotherapy was administered immediately after haemodialysis, except in patients who received cyclophosphamide (n = 5) where haemodialysis was started 8–12h after cyclophosphamide to eliminate toxic metabolites. A standard dialysis regime was used in all patients as follows: 4h three times a week with a polysulfone low-flux filter, blood flow 200–300 ml/min, dialysate flow 500 ml/min.

The outcome was assessed by clinical response to therapy, improvement of surrogate laboratory values, tumour response and survival time from diagnosis of the malignancy. Survival time was defined as the interval between the first diagnosis of the malignancy and death.

Pharmacokinetic models and dose adjustment

Dosages were given in agreement with standard protocols or individually adjusted to the general condition of the patient and stage of the malignancy. The administered dose was decided by the responsible oncologist and nephrologist based on clinical judgement and pharmacokinetic data if available. The administered doses were compared with the theoretically derived proposals calculated by the Dettli rule [9] and the Giusti and Hayton approach [10] using pharmacokinetic data from the literature [11]. Dettli’s proportional dose reduction rule is given in equation 1 (for symbols see Table 1):

\[
\text{Dose/Interval} = \left(\text{Dose/Interval}\right)_{\text{norm}} \times \left(\frac{T_{1/2}}{T_{1/2}^{\text{norm}}}\right)
\]

The Giusti and Hayton approach is based on the fraction of the drug eliminated by the renal route [10]. Consistent with the Dettli concept [9], we also estimated the fraction \(f_{\text{ren}}\) from the half-life values (Table 1) and vice versa (\(f_{\text{ren}} = 1 - \left(\frac{T_{1/2}}{T_{1/2}^{\text{norm}}}\right)\)).

\[
D = D_{\text{norm}}\left(1 - f_{\text{ren}}\left(1 - \frac{Cl_{\text{C1}}}{Cl_{\text{Cnorm}}}\right)\right)
\]

Laboratory and clinical parameters were compared before and during chemotherapy with non-parametric tests. Statistical significance for all tests was set at a level of \(P < 0.05\). No adjustment for multiple comparisons was done, so significant results were interpreted in an exploratory manner. Median survival time was calculated by Kaplan–Meier analysis. All statistical analyses were done using the SPSS 8.0 software package (SPSS Inc., Chicago, IL). Data are given as mean values with 1 SD or as median values with minimum and maximum.

Results

Between 1985 and 2001, 16 patients (nine males and seven females) were recorded with end-stage renal disease on haemodialysis before diagnosis of the malignancy (nine haemoblastic and seven solid malignancies). The 16 enrolled patients were treated with 21 chemotherapy protocols (48 cycles). Those patients with haemoblastic tumours included five multiple myeloma, one Hodgkin’s disease, one Burkitt’s lymphoma, one with low-grade B-cell lymphoma, and one acute myeloid leukaemia. The patients with solid tumours were two with colon carcinoma, two with breast cancer, one with pancreatic carcinoma, one with small-cell lung cancer and one with non-small-cell lung cancer. The mean age of the patients was 55±17 years at the beginning of haemodialysis and 58±11 years at the diagnosis of malignancy. The median body mass index at the beginning of chemotherapy was 22 kg/m^2 (range 16–29 kg/m^2). Chemotherapy started within 2 weeks after diagnosis of malignancy in all patients.

Response to chemotherapy and survival of the patients

Overall, the median Kaplan–Meier survival time was 22 months after diagnosis of malignancy (range 3 to >80 months). Two patients were alive at the end of the observation period. In the nine patients with haemoblastic malignancies, the median survival was 30 months (range 3 to >80 months). One patient with Hodgkin’s disease was in complete remission after >4 years. In the seven patients with solid malignancies, the median survival time was 10 months (range 8 to >80 months). One patient with breast cancer was in partial remission after >6 years.

Dose adjustment

On average, the administered dose was reduced to 91% of the standard dose; however, this reduction
was still 19\% higher than the proposed dose as calculated by the Dettli rule (Table 1). In 10 out of 21 chemotherapies, the dose was reduced initially, whereas 11 chemotherapy regimens were initially administered with the standard doses. The doses of subsequent cycles were adapted with regard to the blood cell count and adverse events. In two patients, subsequent doses were increased up to the regular dosage, since no side effects were observed. No patient required a further reduction of subsequent doses. Chemotherapy was administered at the usual dose interval in all patients. The chemotherapy regime was changed in three patients because of tumour progression and in one patient because of leukopenia.

Three of our patients with haemoblastic malignancies and high dose chemotherapy died from infection. None of our patients with solid malignancies died from infection during therapy-associated leukopenia. We observed severe leukopenia in one patient with an unreduced polychemotherapy of carmustine, etoposide, cytarabine and melphalan (DEXA-BEAM protocol). Severe nausea was observed in only one patient. Pulmonary toxicity, cardiotoxicity or neurotoxicity was not observed. None of the patients suffered from severe mucositis. Anti-emetic prophylaxis was usually effective with metoclopramide (30 mg/day), ondasetrone or corticosteroids.

**Discussion**

Formerly, cytotoxic drugs with mainly renal elimination or high dose chemotherapy protocols were not administered to haemodialysis patients due to the
presumed risk of prolonged leukopenia and severe myelotoxicity. We demonstrated with our analysis that chemotherapy is feasible in patients on haemodialysis without unpredictable severe side effects. The task is to find dose adjustment models for cytotoxic drugs and to modify existing chemotherapy protocols adequately for patients receiving haemodialysis. Blood concentration monitoring and target range-based methotrexate dose adjustment according to individual renal function and drug clearance can significantly improve survival outcome, as has been shown in childhood leukaemia [12].

The administered dosages were found to be significantly higher than the proposed adjustments according to Dettli’s proportional dose reduction rule. We have supplemented the dose calculated by Dettli’s rule to replace the drug elimination by haemodialysis. The effect of haemodialysis on carboplatin kinetics is found to be considerable, but not on etoposide kinetics [13]. We even increased the initial doses in two cycles. Overall, in 28 cytotoxic drug cycles, the administered dosage was significant higher (119%) than that suggested by Dettli’s rule ($P < 0.01$). Also for antimicrobial drugs, dose proposals based on Dettli’s rule were also found to be too low in patients with renal impairment [14].

The Giusti and Hayton model is based only on the renally eliminated fraction of the unchanged drug as determined in patients with normal renal function. With the Dettli rule, in contrast, the clearance or half-life values can be used as determined in a renal failure patient population. Dettli’s rule is helpful in the prevention of severe haematotoxic effects of cytotoxic drugs with a total renal elimination of $> 30\%$. We administered cisplatin to one patient with a small dose reduction to still 80% of the regular dose, in contrast to 53% calculated by Dettli’s rule. In patients with lung cancer, blood concentration monitoring was performed, and the fraction of free cisplatin and total cisplatin removed by haemodialysis was calculated as $87 \pm 22$ and $44 \pm 12\%$, respectively [5]. Haemodialysis in this trial was performed immediately after the administration of cisplatin. In contrast, our patient received cisplatin chemotherapy after dialysis.

Patients on haemodialysis have a significantly higher mortality risk due to sepsis [4]. Three of our patients with haemoblastic malignancies and high dose chemotherapy died from infection. Overall, the progression of the malignancy was the main lethal event in our patients, and progression was associated with a Karnofsky index below 40% in six patients.

The median survival of our patients with multiple myeloma was 30 months. The survival of patients with multiple myeloma and renal failure is reported as 2 months without chemotherapy, 10 months with vincristine, Adriamycin and dexamethasone therapy, and 12 months with melphalan protocols [15]. Successful autologous stem cell transplantation has been performed recently with higher dose melphalan in haemodialysis patients [16,17].

In conclusion, chemotherapy can be administered to haemodialysis patients with a predictable risk of side effects if individual dose adjustment is performed. We have seen the need for pharmacokinetic-guided and individually adjusted chemotherapy in patients treated with haemodialysis—a complex procedure with many variables, differing from one clinic to another. To select the adequate dose still needs the decision of experts in oncology and nephropharmacology, since no algorithms and no evidence are at hand yet. It is still necessary to prove the effectiveness of chemotherapy in these selected patients and to collect the further data necessary for pre-treatment dose adjustment.

Conflict of interest statement. None declared.

References


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