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Renal complications in acute leukemias

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ABSTRACT

Background and Objective. **Renal failure is a known complication of acute leukemias both at diagnosis and following cytostatic treatment. No recent studies give data on the incidence and risk factors of renal complications and their prognostic impact.**

Design and Methods. **Two hundred and twenty consecutive adult patients with newly diagnosed acute leukemia treated at a major university medical center were evaluated for renal complications before, during, and after treatment; 166 patients were treated by chemotherapy only and 54 patients were treated with chemotherapy and later transplanted with allogeneic or autologous bone marrow. Renal complications were subdivided into 3 entities: acute renal failure, major and minor complications, based on clinical and laboratory parameters. Renal failure occurring as a consequence of terminal multi-organ failure was excluded from the present study.**

Results. **Approximately 30% of patients in the chemotherapy group had a renal complication either before or after chemotherapy. Patients undergoing transplantation had a 50% risk of renal complications. Risk factors for complications were male sex, age, previous kidney disease, white cell count, and refractory leukemia (chemotherapy group) and allogeneic versus autologous transplant (transplant group). In the chemotherapy group, early but not delayed renal complications had a poor prognostic impact. In the transplant group renal complications had no impact on prognosis. In all patient groups, acute renal failure was prognostically unfavorable.**

Interpretation and Conclusions. **We conclude from our study that renal complications are frequent in acute leukemias and that the treatment and prevention of renal complications is important for the management of acute leukemias.**
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Key words: acute leukemias, renal complications, chemotherapy, bone marrow transplantation

Acute renal failure has been known as a possible complication of leukemias for many years and has been mentioned in numerous case reports,[1-7] but no recent study has systematically examined the incidence, cause and outcome of renal failure or any renal complication in patients with acute leukemias. Several earlier studies showed an adverse influence of renal failure in acute leukemias.[3,8,9] Acute monoblastic leukemia was reported to have a high incidence of renal failure.[10] In acute promyelocytic leukemia, an earlier series reported a 37% incidence of renal failure at presentation or during induction therapy and a poor outcome in almost all cases.[11] An impaired renal function is a well-known complication of cyclosporine A in patients who received bone marrow transplants.[12,13] Renal complications in acute leukemias may be due to preexisting disorders, leukemic infiltration of the kidneys, metabolites of leukemic cells including uric acid and phosphate,[14] nephrotoxic drugs, septicemias and other conditions. During the last thirty years, the prognosis of acute leukemias has improved due to intensive chemotherapy, bone marrow transplantation and better supportive therapy. In this study, we investigated 220 consecutive adult patients with acute leukemias (166 acute myeloid leukemias and 54 acute lymphoid or undifferentiated leukemias, treated with either chemotherapy, or chemotherapy and subsequent bone marrow transplantation) for the incidence, pathogenesis, prognostic impact and the outcome of any renal complication.

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Patients and Methods

Patients

All adult patients (aged 17 years or older) at a major university center diagnosed or referred between 1985 and 1989 with acute leukemia were retrospectively reviewed for renal complications. Follow-up was complete till the death of the patient or until July 1990. The diagnosis of acute leukemia was made according to standard hematological and hematopathological criteria. Acute myelogenous leukemia (AML) was subdivided according to FAB-criteria. Eight patients had FAB-type M1, 20 patients M2, 18 patients M3, 38 patients M4, 24 patients M5 and 4 patients M6 or M7. Acute lymphoblastic leukemias (ALL) and acute undifferentiated leukemias were subdivided according to their immunologic phenotypes. Twenty patients were classified as pre-B-ALL, 11 patients had T-cell markers, 5 patients were B-ALL and 4 remained undifferentiated. Patients with a hypocellular bone marrow, > 20% blasts in the bone marrow, but no significant increase in the blast count after 4 weeks, were categorized as

AML (smoldering variant, 14 patients). Most patients with AML had induction therapy with an anthracycline and standard-dose cytosine-arabinoside. Some elderly patients were only treated with low dose cytosine-arabinoside. Patients with acute acute promyelocytic leukemia were on low-dose heparin during the induction treatment. Most patients with ALL were treated according to BMFT-study protocols.[15] Due to clinical considerations, 14 patients received no cytostatic treatment. Adequate hydration and allopurinol routinely prevented a tumor lysis syndrome. All age categories were represented; 115 patients were male and 105 female. All patients were asked about previous kidney disease, 30 patients had a history of kidney stones, pyelonephritis, prostatic adenoma or carcinoma, ureter stenosis or other problem of the genito-urinary tract. No patient was in chronic renal failure or on hemodialysis, before acute leukemia was diagnosed.

Refractory leukemias were diagnosed when no remission (< 5% blasts in bone marrow, adequate recovery of peripheral counts), was obtained after 2 months of standard chemotherapy.

Fifty four patients were treated by bone marrow transplantation (44 allogeneic and 10 autologous). 45 of these patients were transplanted in complete remission, 9 patients were in relapse or had refractory leukemia. Patients transplanted with allogeneic marrow were conditioned with 3×4 Gy total body irradiation and cyclophosphamide. Prophylaxis against graft versus host disease was made with cyclosporine A. If indicated, other immunosuppressive agents were used (steroids, monoclonal T-cell antibodies and others). Three patients were transplanted twice with bone marrow. For autologous transplants, marrow was frozen with dimethylsulfoxide and preserved in liquid nitrogen.

Renal complications

Renal complications were graded according to clinical and laboratory criteria. For patients without preexisting renal disease, 3 degrees of renal complications were defined (the cut-off values of creatinine were chosen arbitrarily to select patient with less and more severe impairment):

- minor impairment: increase of serum creatinine > 1.4 but below 2 mg/dL, and/or increase of serum urea > 65 but below 95 mg/dL, and/or decrease of creatinine clearance to values below 85 but still above 70 mL/min.
- major impairment: increase of serum creatinine > 2 mg/dL, and/or serum urea > 95 mg/dL and/or decrease of creatinine clearance below 70 mL/min, but not meeting the criteria of acute renal failure.
- acute renal failure (anuria, oliguria).

Normal values were: 0.5-1.1 mg/dL for creatinine, and 10- 50 mg/dL for serum urea. For the diagnosis of a renal complication, the laboratory values had to be pathological on at least 2 separate days.

The duration of a renal complication was scored until the pathological parameters had normalized for at least one week. If the renal function was again impaired thereafter, a new renal complication was diagnosed. The onset of a renal complication was also determined: at diagnosis or within 7 days of starting chemotherapy, or later. A different time frame was used for patients who underwent bone marrow transplantation: before or during conditioning, during the first 100 days after transplantation, or later. An impaired renal function observed in multiorgan failure within 7 days of death was categorized as terminal renal failure and was not included in the above tabulation.

A lethal outcome of a renal complication was by definition death within 90 days after the onset of a renal complication, which had not normalized, and was not directly caused by leukemia.

Statistical analysis

Differences between groups were compared with Fisher's exact (two-sided) and χ^2 test. The influence of continuous parameters was estimated with the parameter-free test of Wilcoxon. The survival of different groups was calculated with a Kaplan-Meier analysis (log rank comparison).

All statistical analysis was done with SAS software (release 6.11). Features independently associated with overall survival were identified in multivariate analyses by proportional hazard regressions. Step-down regression methods were used to build parsimonious statistical models for the association of prognostic factors with overall survival among patients with complete data.

Results

Incidence and severity of renal complications

Among the total group of 220 patients, 166 were treated with chemotherapy and 54 underwent bone marrow transplantation. A flow-sheet for both groups of patients is given in Figure 1. Both categories of patients are analyzed separately, since both have a different age, general condition and risk of leukemic relapse. In the group of patients treated with or intended for chemotherapy, 50 patients (31%) had 62 renal complications. Thirty patients had these complications before chemotherapy was started and 30 patients later (10 patients had complications both before and after the start of chemotherapy). As can be seen in Figure 1, a total of 14 cases of acute renal failure (ARF), 18 cases of major and 30 cases of minor complications occurred. Among the patients treated with a bone marrow transplant, 27 patients (50%) had renal complications, 4 patients before, 23 patients between day 0 and 100 after the bone marrow transplant and 4 patients later (4 patients had complications during more than one period). As can be seen in Figure 1, a

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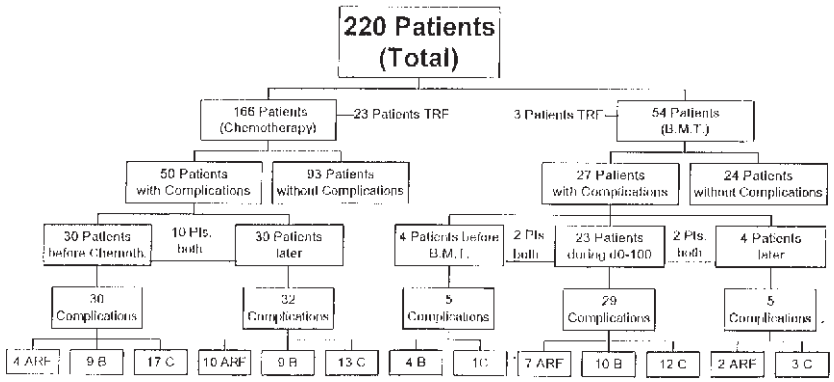

Figure 1. Flow sheet for the development of renal complications in patients with acute leukemias treated by chemotherapy or bone marrow transplantation.
Abbreviations: TRF. terminal renal failure, ARF: acute renal failure, B.M.T.: bone marrow transplantation, B: major complication, C: minor complication.

total of 39 complications were observed, split into 9 cases of ARF, 14 major and 16 minor complications.

Risk factors for renal complications

In the group of patients treated or intended to be treated by chemotherapy, risk factors for early complications were male sex, advanced age, history of previous kidney disease, and refractory leukemia (see details in Tables 1 and 3). A high white cell count had an especially high risk for renal complications. Patients with early complications had a median white cell count of 127 k/ul, compared with 44 k/ul in patients without early complications ($p < 0.001$). Only male sex was also a risk factor for later complications, especially increasing the risk of acute renal failure (17/23 cases in the total group). The type of leukemia (AML or ALL, see Table 1) had no significant influence on the frequency of renal complications. The subclassification of AML or ALL also had no influence on the risk of early or late complications, especially monoblastic leukemias, which were not associated with an increased risk for kidney dysfunction (data not shown).

In the transplant group, only the type of transplant (allogeneic versus autologous) had an influence on the risk of renal dysfunction (see Table 2, 4 patients with complications before transplantation are not included in Table 2). As in the chemotherapy group, the subtypes of AML or ALL did not influence the risk for kidney dysfunction (data not shown).

Table 1. Risk factors for renal complications in patients treated with chemotherapy.

Parameters Risk Factors	*No. of patients*	*Patients with complications before CT*		*Patients with complications after CT*	
Leukemia type					
AML	126	19 (15%)		23 (18%)	
ALL/AUL	40	11 (28%)	n.s.	7 (18%)	n.s.
Sex					
Male	85	24 (40%)		22 (26%)	
Female	81	6 (7%)	p< 0.001	8 (10%)	
p=0.007					
Refractory?					
Yes	15	12 (40%)		5 (33%)	
No	151	18 (14%)	p=0.021	27 (20%)	n.s.
Renal history?					
Yes	30	12 (40%)		9 (30%)	
No	133	18 (14%)	p<0.001	27 (20%)	n.s.
Age					
17- 44 years	51	4 (8%)		8 (16%)	
45 years or older	115	26 (23%)	p<0.001	22 (19%)	n.s.
White cell count at diagnosis					
	166 (total)	high vs. low	p<0.001	high vs. low	n.s.

Pathogenesis of renal complications

We attempted to correlate the renal dysfunction with a likely cause. Before the chemotherapy was started, in 5/30 cases the decrease in renal function was related to a preexisting condition. The other cases were obviously related to the proliferation of leukemic blasts, although the pathomechanism was not directly studied. At the later period, most instances of renal dysfunction were related to drugs, the lysis of leukemic cells or a combination of both (17/32 cases, 53%). Drugs commonly administered before a renal complication developed were aminoglycosides and amphotericin B. In patients treated with bone marrow transplants, a different spectrum of likely causes was observed: in the early period (up to day 100), 24 cases (83%, including 5 cases of acute renal failure) were related to drug toxicity (mainly cyclosporine A) and/or microangiopathy and/or graft-versus-host disease-related complications. One patient had an aggravation of a pre-existing condition. During the later period (beyond day 100), again 8/10 complications were related to a likely drug toxicity.

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Table 2. Risk factors for renal complications in patients treated with bone marrow transplantation.

Parameters Risk Factors	*No. of patients*	*Patients with complications between d0 and d100 after BMT*		*Patients with later complications*	
Leukemia type					
AML	40	16 (40%)		6 (18%)	
ALL/AUL	14	7 (50%)	n.s.	0	n.s.
Sex					
Male	30	12 (40%)		2 (6%)	
Female	24	11 (46%)	n.s.	4 (16%)	
p=0.007					
Type of transplant					
Allogeneic	44	12 (50%)		6 (13%)	
Autologous	10	1 (10%)	p=0.031	0	n.s.
Age					
17- 44 years	45	21 (49%)		2 (5%)	
45 years or older	9	2 (22%)	n.s.	2 (22%)	n.s.
White cell count at diagnosis					
	54 (total)	high vs. low	n.s.	high vs. low	n.s.

Table 3. Outcome of chemotherapy in patients with and without renal complications at diagnosis.

Group of patients	*a. Achieving complete remission*	*b. Failing induction treatment*	*c. Not evaluable*
Renal complications at diagnosis (n=30)	8/23 (34.8%)	15/23 (65.2%)	7/30 (23.3%)
No renal complications at diagnosis (n=136)	88/118 (74.6%)	30/118 (25.4%)	18/136 (13.2)

Outcome of renal complications

Patients with acute renal failure generally were treated with hemodialysis and/or hemofiltration. In cases of lesser degree of renal impairment, the presumed causative factors were eliminated, if possible. In the chemotherapy group, 2/4 cases of early ARF were lethal and 4/10 cases of later ARF ended lethally. The 2 other cases of ARF (early group) led to chronic compensated renal injury (2/10 in the later group). Lesser degrees of renal injury most often normalized (81% in the early group, 76% in the later group). Nevertheless, even 3/21 cases with minor or intermediate complications ended lethal. In the transplant group, 1/7 early cases of ARF and 1/2 cases of later ARF ended with the patient's death despite adequate therapy. Cases of minor or major impairment of renal impairment most

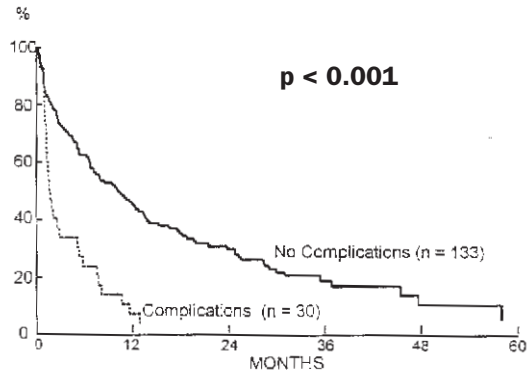

Figure 2. Survival of patients with acute leukemias and a renal complication before start of chemotherapy compared with patients without a renal complication.

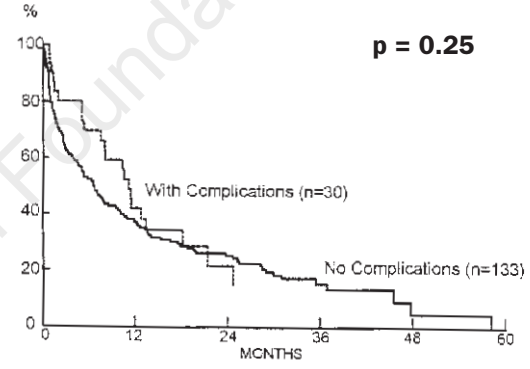

Figure 3. Survival of patients with acute leukemias and a renal complication after the start of chemotherapy compared with patients without a renal complication.

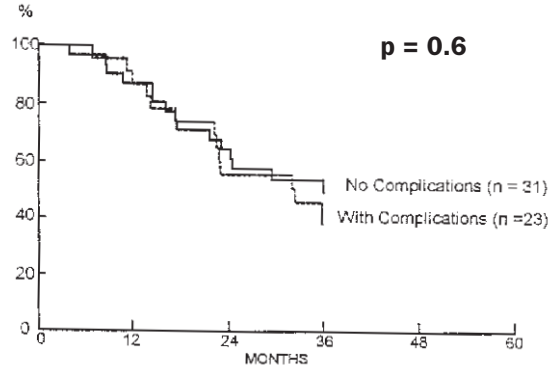

Figure 4. Survival of patients with acute leukemias treated with a bone marrow transplant and a renal complication during the first 100 days after the transplant in comparison with patients with no renal toxicity.

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often normalized (68% in the early, 100% in the later group), although some cases (2 respectively 5 cases among 22 complications) were lethal or resulted in chronic compensated renal injury.

Impact of renal complications on prognosis

In the chemotherapy group, patients with early complications (all degrees of renal impairment taken together) definitely had a less favorable outcome in comparison with patients with normal renal function (See Figure 2). All 4 cases of early ARF had a fatal outcome within 4 months. Patients with a renal complication at diagnosis tended to have a lower rate of complete remission compared with patients without renal dysfunction (See Table 3). A multivariate analysis of the survival data in Figure 2 showed that renal failure was an independent prognostic factor (examined for age, sex, leukocyte count). In the patients who had complications after the chemotherapy was started, no clear difference existed in comparison with patients who continued to have a normal renal function (See Figure 3). In the transplant group, due to aggressive management and the frequent reversibility of renal impairment, no survival difference was observed in patients with and without early complications if all degrees of renal impairment are considered (see Figure 4). However, ARF clearly had an unfavorable prognostic impact, with no patient surviving more than 36 months. Beyond day 100 after transplantation, renal complications were less frequent and had no clear impact on prognosis (data not shown).

Discussion

In some but not all earlier studies, renal failure was described as an unfavorable prognostic criterion in patients with untreated AML.[8,16-18] Few studies analyzed the incidence of renal failure in unselected patients. One study mentioned an incidence of 15% of elevations of creatinine in untreated AML patients.[16] In a more recent study in untreated ALL, an incidence of 13 respectively 25% was noted depending on the age below or above 60 years.[19] In the subtype of acute monoblastic leukemia, renal impairment was found in as frequently as 40% of untreated patients.[10]

The present study identified a renal complication before treatment in 30/166 patients (18%). Due to the positive selection of patients who later received a bone marrow transplant, only 4/54 of such patients (7%) had a complication before their disease was initially treated. In our group of patients, the risk factors for renal failure correspond to other common risk factors in acute leukemia (high white cell count, advanced age, male sex). Previous kidney disease also increases the risk for a renal complication. To some extent chronic obstruction due to prostate enlargement, may have increased the risk for renal dysfunction in older male patients. The subtype of leukemia did not increase the risk of kidney dysfunction. Beyond the presentation and excluding terminal renal failure from other causes, 32 renal complications were also observed in 30 patients (incidence 18.6% among 161 patients surviving at least 7 days). These complications were in general multifactorial. A tumor lysis syndrome which is a well known complication in children with ALL[5,20] was rare in the present series and not the only cause of impaired renal function. Taken together, in our series 50/166 (30%) adult patients developed a renal complication during the course of their disease. Acute monoblastic or myelomonoblastic leukemia was not associated with a particular risk of early or later renal failure. In the group of leukemia patients treated with bone marrow transplantation, an impaired renal function was frequent during the early transplant period, especially in allogeneic transplants (50% incidence) and procedure-related.

Previous studies mentioned drug toxicity,[12,23] microangiopathy as a consequence of endothelial damage,[13] viral infections,[24] radiation nephritis[25] and autoimmune phenomena[26] as causes of renal failure during and after bone marrow transplantation. In an earlier original study comparing cyclosporine to methotrexate as graft-versus-host-disease prophylaxis, 58% of cyclosporine treated patients had a major renal complication.[27] The lower number in the present series (15/44 allogeneic transplant recipients, 34%, had 17 major complications) appears to be due to improved supportive therapy with frequent monitoring of cyclosporine levels. In children with acute lymphoblastic leukemia, a delayed onset of renal dysfunction was described. This complication occurred 36 months after an autologous transplant and had also features of microangiopathy.[21] In a recent study, a high incidence of delayed renal dysfunction was reported after allogeneic transplants (up to 45% after 18 months).[22] This delayed toxicity was associated with a higher dose of total-body irradiation (13.5 Gy) than used in the present series. The pathogenetic factors involved in acute renal failure occurring in the setting of bone marrow transplantation were recently reviewed.[23]

In the present series, few patients had delayed or late renal toxicity. In the total group of patients with acute leukemia, a renal complication before treatment is clearly an unfavorable prognostic sign. Acute renal failure has an especially poor prognosis. However, the complication is disease-associated and most cases require aggressive management.

Two previous studies examined the outcome of acute renal failure in patients with hematological malignancies.[3,9] In these studies, 45 and 35%, respectively, of the patients survived the episode of renal failure. In the present series the immediate prognosis appears better (15/23 patients, 65% recovered their renal function). However, this may be related to different patient groups studied and the exclusion of patients in multiorgan-failure who rarely recover. During and after chemotherapy, a renal complication by

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itself has no negative influence on prognosis. The same is true for renal complications occurring during and after bone marrow transplantation with the exception of acute renal failure. Taken together, renal complications are frequent in acute leukemia. In high-risk patients, nephrotoxic drugs and antibiotics should be avoided. Renal parameters should be monitored frequently to avoid acute renal failure which is prognostically unfavorable in all patient categories. The recognition, treatment and prevention of renal complications are important for the management of acute leukemias.

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Disclosures

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