# Intensive care of haematological patients

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## ABSTRACT

**INTRODUCTION:** This article presents the treatment results of 320 consecutive patients with malignant haematological diagnoses admitted to a tertiary intensive care unit at a Danish University hospital over a six-year period (2005-2010). With reference to international publications, we describe the development in treatment.

**MATERIAL AND METHODS:** This was a retrospective observational study.

**RESULTS:** The median age was 59 years. The median intensive care unit (ICU) stay was six days. A total of 88% required mechanical ventilation, and 72% received vasopressor treatment. The median Simplified Acute Physiology Score II score was 58. The ICU and one-year mortality rates were 44% and 77%, respectively, but mortality was significantly lower for patients aged 0-20 years. For patients aged 20-80 years, the mortality risk was independent of age. For the group of patients admitted acutely to the ICU with other diagnoses, the ICU- and the one-year mortality rate was 13% and 33%, respectively.

**CONCLUSION:** Despite progress, the mortality rate for haematological patients in ICUs is high. We lack valid tools that allow us to differentiate between those who can benefit from intensive care and those for whom transfer to an ICU is futile. One patient out of five is alive after one year. This supports a strategy offering haematological patients intensive care on an equal footing with other patients. Follow-up studies of survivors, clarification of function level and quality of life are needed.

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In the past decades, considerable progress has been made in haematology and intensive care. An increased understanding of various disorders and efficient symptomatic and causal treatment have significantly reduced mortality. Thus, valid therapeutic options are being offered to more patients.

The mortality rate for haematological patients requiring intensive care is, however, still significantly higher than that of the majority of other intensive care unit (ICU) patients. This article presents the treatment results for haematological patients admitted to a multidisciplinary ICU in a tertiary university hospital over a six-year period. With reference to international publications, we describe the development in treatment.

## MATERIAL AND METHODS

The present study was a retrospective observational study of patients admitted to the Department of Intensive Care 4131, Rigshospitalet, from 1 January 2005 to 31 December 2010. Data were collected from the department's Critical Information System (CIS) (Daintel) and from GS Open. All patients with malignant haematological diagnoses were identified and stratified into four main groups: leukaemia, malignant lymphoma, multiple myeloma, and myelodysplastic syndrome. (Leukaemia: leucaemia myeloides chronica, leucaemia myeloblastica acuta, leucaemia lymphatica chronica, leucaemia lymphoblastica acuta, leucaemia non specificata. Malignant lymphoma: lymphoma malignum non Hodgkin non specificata, lymphoma malignum (B-cell) non specificata, lymphoma malignum (T-cell) non specificata, lymphoma Hodgkin non specificata. Myelomatosis and myelodysplastic syndrome). Variables collected included: sex, age, duration of ICU stay, respiratory failure (need for mechanical ventilation), circulatory failure (need for vasopressors), mortality and Simplified Acute Physiology Score (SAPS) II. For patients admitted more than once during this period, only data from the first hospitalization were registered.

The control group comprised data for all other patients admitted acutely to the ICU during the same period.

Descriptive statistics were calculated in SAS 9.2. Continuous data are reported as medians with interquartile ranges and dichotomous variables as proportions. Confidence intervals of proportions are based on normal approximation, which we tested for in each calculation. P values were calculated using Fisher's exact test.

*Trial registration:* not relevant.

## RESULTS

During the study period, a total of 320 patients with a malignant haematological disorder had a first-time admission to the ICU (**Table 1**). Twice as many men as women were admitted. The median age was 59 years and it remained constant during the study period. The median ICU stay was six days. Sixty-four patients (20%) were in the ICU between two and six weeks, and 15 patients (5%) were in the ICU for more than six weeks. Half of the patients had leukaemia. In the ICU, 88% required

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TABLE 1

Patient characteristics.

| | |
|---|---|
| Patients, n | 320 |
| *Sex, n (%)* | |
| Female | 105 (33) |
| Male | 215 (67) |
| *Age, n (%)* | |
| 0-20 years | 39 (12) |
| 21-40 years | 29 (9) |
| 41-60 years | 101 (32) |
| 61-80 years | 149 (47) |
| > 80 years | 2 (>1) |
| Age, years, median (interquartile range) | 59 (44.5-65) |
| Hospitalization period, days, median (interquartile range) | 6 (2-14) |
| *Type of malignancy, n (%)* | |
| Leukaemia | 157 (49) |
| Malignant lymphoma | 94 (29) |
| Multiple myeloma | 45 (14) |
| Myelodysplastic syndrome | 24 (8) |
| *Mortality, n (%; 95% CI)* | |
| ICU | 141 (44; 39-50) |
| 30-day | 169 (53; 47-58) |
| 90-day | 208 (65; 60-70) |
| 365-day[a] | 242 (76; 72-81) |
| *Organ failure in the ICU, n (%)* | |
| Respiratory failure | 281 (88) |
| Circulatory failure | 229 (72) |
| SAPS II, median (interquartile range)[b] | 58 (47-71) |
| SAPS II predicted mortality, % | 64 |

CI = confidence interval.; ICU = intensive care unit.; SAPS = Simplified Acute Physiology Score.

a) The 365-day mortality was followed until 1 December 2011. The 365-day status is lacking for three of 320 patients (all three with leukaemia).

b) SAPS II was calculated for 247 patients. SAPS II was not calculated for patients less than 15 years of age or for patients hospitalized for less than 24 hours. A total of 31 patients were under 15 years of age, 39 patients were hospitalized for less than 24 hours and three patients had missing data for unknown reasons

TABLE 2

Mortality according to diagnosis.

| | Patients, n | ICU mortality, % | 30-day mortality, % | 90-day mortality, % | 365-day mortality,[a] % |
|---|---|---|---|---|---|
| Leukaemia | 157 | 49 | 53 | 64 | 73 |
| Malignant lymphoma | 94 | 45 | 57 | 68 | 78 |
| Multiple myeloma | 45 | 31 | 44 | 58 | 73 |
| Myelodysplastic syndrome | 24 | 33 | 50 | 75 | 96 |
| Total | 320 | 44 | 53 | 65 | 76 |

ICU = intensive care unit.

a) The 365-day mortality was followed until 1 December 2011. The 365-day status is lacking for three of the 320 patients (all three with leukaemia).

mechanical ventilation and 72% received vasopressor treatment. SAPS II values were recorded in 247 patients. They had a median score of 58, which corresponds to an expected hospital mortality rate of 64%. The ICU mortality and one-year mortality rates were 44% and 77%, respectively (Table 1). Patients aged 0-20 years had a significantly lower mortality rate in the ICU (28% versus 46%, p = 0.04) and 365 days after admission (51% versus 80%, p < 0.001). For patients aged 20-80 years, the mortality risk was independent of age (p = 0.51). Patients with leukaemia and malignant lymphoma had the highest ICU mortality rates (49% and 45%, respectively). Patients with myelodysplastic syndrome had a better survival rate in the ICU (33% died) than the other stratified groups, but had the highest long-term mortality rates after 90 days (75%) and 365 days (96%) (**Table 2**). Circulatory and respiratory failures were both strong risk factors for ICU mortality (**Table 3**).

The ICU mortality rate for patients with a haematological disorder was three times as high as in the rest of the group of patients admitted acutely to the ICU (44% versus 13%). The one-year mortality rate for the haematological patients was 77%, compared with 33% for the group of other patients (**Table 4**).

## DISCUSSION

### Trends in haematological treatment

Within the past decade, a significant improvement has been noted in the five-year survival rate for patients with a number of haematological disorders. For non-Hodgkin lymphoma, the largest malignancy group, the five-year survival rate is currently 81% compared with 65% in the 1999-2004-period. The improved survival rate can partly be ascribed to administration of the monoclonal anti-CD20 antibody in chemotherapy regimens ("immunochemotherapy") and the more widespread use of high-dose chemotherapy with stem cell transplantation [1]. For patients with acute myeloid leukaemia, the current five-year survival rate is 50% for patients under 60 years of age compared with 40% in 2006; a change which has mainly been achieved owing to improved supportive care. No change has been observed in the survival rate for patients with acute myeloid leukaemia above 60 years of age (five-year survival at about 10-15%) [2]. Multiple myeloma is still an incurable haematological disorder, but the standard treatment of high-dose chemotherapy with autologous stem cell support has improved the five-year survival rate to approx. 73% for patients less than 65 years of age compared with less than 50% in 2000 [3]. For patients with chronic lymphocytic leukaemia and low-grade lymphoma, non myeloablative stem cell transplantation is now a potentially curative treatment offered to patients with a fairly advanced disorder who were previously incurable.

In general, the prognosis in all groups is significantly poorer in patients over 65 years of age. Older patients have a higher level of co-morbidity, an increased treatment-related mortality and a higher incidence of relapse.

Haematological disorders per se and several of the treatment regimens used can affect organs and reduce immunity. This may elicit organ failure, typically in the form of septic shock or respiratory failure, and intensive care may be required.

**Treatment results in the intensive care unit**

The high ICU, 90-day, and 365-day mortality rates among haematological patients in ICU is well-documented [4-7] and may be explained by the underlying disease, the degree of acute disorder and treatment-induced side-effects. In a French study comprising 124 patients comparable to ours, ICU mortality rates of 42% and a half-year mortality rate of 66% were reported [4]. As in our study, they were not able to demonstrate a correlation between age and mortality in adult patients. This probably reflects a stringent selection of patients evaluated for intensive care. Patients with a limited potential for treatment and a poor short-term prognosis remain in the wards for palliative treatment. The significantly better survival rate for patients under 20 years of age is attributed to the better prognosis for very young patients with acute leukaemia. Patients with myelodysplastic syndrome had a high 365-day mortality rate (96%), probably because they were progressing to acute myeloid leukaemia. It is well known that once transformation into an acute leukaemia has occurred, these patients respond poorly to intensive chemotherapy and have a high mortality rate.

Our study is limited to data available in the Intensive Care Department's CIS (Daintel) and GS Open. The CIS has been upgraded regularly, but for the period in question, lab results and bone-marrow transplantations, for example, were not consistently registered. This limits relevant subgroup analyses.

A number of prospective and retrospective studies comparing two time periods in subgroups of cancer patients treated in ICUs have demonstrated better hospital survival in the past decade than previously [8, 9]. These studies, including the present study, are typically single-centre studies based on patient material of considerable heterogeneity. Different criteria for admission to intensive care and discharge make comparison difficult. No specific cause for the falling mortality rate has been identified. Azoulay et al have summed up a number of plausible explanatory hypotheses [10, 11]: 1) General improvements in chemotherapy treatment, specific therapy and supportive treatment. 2) Better insight into the optimal time for treatment. 3) General improvements in intensive care, including improved circulatory treatment for patients in septic shock, the use of non-invasive ventilation and better insight into a number of pathophysiological conditions in critically ill patients. 4) Improved ways of demonstrating aetiological reasons for respiratory failure. 5) A possible change in the triage practice to ICU.

TABLE 3

ICU mortality according to circulatory and respiratory failure.

| | ICU mortality, % (n/N) | p values |
|---|---|---|
| *Mechanical ventilation* | | $< 10^{-3}$ |
| Yes | 50 (140/281) | |
| No | 3 (1/39) | |
| *Treatment with vasopressors* | | $< 10^{-3}$ |
| Yes | 53 (123/230) | |
| No | 20 (18/90) | |
| None of the above | 4 (1/28) | $< 10^{-3}$ |
| One of the above | 23 (17/73) | |
| Both of the above | 56 (123/219) | |

ICU = intensive care unit.

TABLE 4

Mortality statistics for haematological patients treated in the ICU at Herlev Hospital (1992-1994) and Rigshospitalet (2005-2010), respectively, and mortality statistics for other acute admissions to the ICU at Rigshospitalet (2005-2010).

| | Patients, n | ICU mortality, % | 90-day mortality, % | 365-day mortality, % |
|---|---|---|---|---|
| *Herlev Hospital* | | | | |
| Haematological patients | 68 | 56 | 72 | 78 |
| *Rigshospitalet* | | | | |
| Haematological patients | 320 | 44 | 65 | 77 |
| Other acute admissions | 4,366 | 13 | 27 | 33[a] |

ICU = intensive care unit.
a) 365-day mortality for 2005-2009 (3,564 patients in all), due to incomplete 365-day status for 2010.

We have compared our results with data on haematological patients from the ICU at Herlev Hospital, (Table 3) [12], where the observation period was three years (1992-1994). No difference in ICU, 90-day, and 365-day mortality rates could be demonstrated. A direct comparison, however, is not possible as we do not have demographic data, treatment protocols or information on the degree of acute disorder among patients at Herlev Hospital. In our opinion, presentation of absolute survival rates still makes sense, since they reflect the results of the treatment protocols that were used in the observational periods. The unaltered mortality in the two groups, however, contrasts with the results found in international publications.

**Triage to intensive care unit**

Several studies have attempted to identify prognostic factors in patients with malignant disorders evaluated for ICU treatment in order to identify those patients who will benefit from intensive care. The type of underlying cancer, its dissemination, its response to chemotherapy and the presumed long-term prognosis do not

Glass mosaic at the entrance to the Intensive Care Unit, 4131, Rigshospitalet.

correlate with ICU mortality [13]. This can, in part, be explained by selection bias among oncologists and haematologists. The results are contradictory for other classical markers such as age, neutropenia and bone-marrow transplantation [4, 7, 14, 15]. This may be due to a heterogeneous patient material and differences in local guidelines for transferral to ICU.

Evidence-based clear-cut recommendations on ICU admission do not exist. Although in cases of acute deterioration it is difficult to judge who would benefit from intensive care, several studies have found that deterioration in organ function during the first 3-5 days in intensive care are good predictors of ICU mortality [16]. A pragmatic approach is frequently used [10]: Patients who recently began first-line chemotherapy, patients with low-grade haematological malignancies and patients with partial remission are always admitted and given full-code status. Patients with uncertain benefit from intensive care are admitted and given full-code status. For this group, discontinuation of treatment is considered after 3-5 days if there is deterioration or no improvement. Patients who were already chronically, severely debilitated in the ward or for whom there is no further life-prolonging causal treatment are not offered intensive care. In cases of doubt, e.g. in case of acute deterioration during night shifts, patients should be transferred to the ICU. Re-evaluation can be performed in the daytime after initial treatment.

When indicated, early transfer is recommended since ICU mortality rises in keeping with the number of organ failures at the time of ICU transfer [5]. Studies of ICU patients in general show a higher mortality rate for patients with critical illness who are admitted late than for patients who are admitted early [17]. The same is probably true for haematological patients [8].

### Costs associated with intensive care

There has been considerable progress in cancer treatment in recent decades. Technological and pharmacological gains have resulted in more patients surviving or living with cancer. At the same time, the public's treatment expectations have risen. Cancer treatment is being allocated an increasing – and in time perhaps untenable – share of health-care budgets in the Western world. This has resulted in an increased focus on how resources are used. A commission appointed by Lancet Oncology recently published a comprehensive report addressing these issues [18]. One of its findings was the significant overtreatment of dying cancer patients.

Intensive care is expensive. The human costs of intensive care can also be high. Intensive care in general involves the risk of serious side effects, and many patients who survive experience permanent loss of functions.

Nearly half of the haematological patients whom we treat at our ICU die there. The other half survive, thanks to intensive care, but we have no reliable information on their subsequent function level or quality of life. There are no follow-up studies covering this group, neither Danish nor international. We strongly recommend that such studies be performed.

## CONCLUSION

Despite progress, the mortality rate for haematological patients in ICUs remains high. We still lack valid tools for differentiation between those who can benefit from intensive care and those for whom transfer to an ICU is futile. One patient out of five is alive after one year. In our view, this supports a strategy offering haematological patients intensive care on an equal footing with other patients. It is, however, a serious problem that we lack information about the function level and quality of life of survivors. Follow-up studies are necessary in order to clarify this aspect.

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**CONFLICTS OF INTEREST:** none

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