Outcomes of Haematology/Oncology patients admitted to Intensive Care Unit (ICU) at

The Canberra Hospital (TCH)

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Abstract

Background

Outcomes for haematology/oncology patients have improved, however determining their suitability for ICU admission remains challenging and controversial.

Aim

Examine outcomes of patients admitted to an Australian tertiary hospital Intensive Care Unit (ICU) and explore potential prognostic factors.

Methods

A retrospective review of patients with haematological and solid tumour malignancies non-electively admitted to The Canberra Hospital (TCH) ICU, between January 2008 and December 2012. Patient demographics, cancer details, reasons for ICU admission and APACHE II scores were collected and survival rates calculated and correlated with potential prognostic factors.

Results

Of 205 patients, 113 (55%) had haematological malignancies, and 92 (45%) solid tumours; 58% male, and mean age 60.3 years (SD 13.4). 82% of solid tumour patients had metastatic disease and 55% received palliative chemotherapy. Primary reasons for ICU admission included sepsis (59%), respiratory distress (37%) and hypotension/shock (18%). Mean APACHE II score was 20.1(SD 0.55); mean length of stay in ICU, 4 days (SD 5.2); ICU survival was 76% with 62% and 41% alive at 30-days and 6 months respectively.   Overall 1 year survival was 36%. High APACHE II scores and ≥2 organs failing were significant risk factors for 30-day mortality.

Conclusion

Short-term outcomes were similar to contemporary studies from a general tertiary hospital setting and better than historical data. 62% of patients were alive 30 days post-ICU admission, with a significant minority alive at 12 months, confirming some patients achieved worthwhile outcomes. Further research is needed to ensure appropriate patient selection and to explore quality of life post ICU.

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Background:

The overall survival outcomes for oncology patients have greatly improved in recent times, with a 20% decrease in overall mortality between 1978 and 1998 (1). In Australia, between 1982-1987 and 2006-2010, the 5-year relative survival for people diagnosed with cancer increased from 47% to 66% (2), with the largest survival gains over this time seen in prostate cancer, renal cancer and non-Hodgkin's lymphoma, where survival increased from 46.6% to 70.6%. (3). These improvements have been attributed to various factors, including advances in cancer treatment including surgical and radiotherapy techniques, improved supportive care, and aggressive management of malignancy and treatment-related complications.

An important aspect of improving outcomes for patients with malignancy is the provision of critical care during periods of acute deterioration. Intensive care is a costly and limited resource therefore it is important that patients referred for admission are triaged appropriately so that those selected have a reasonable likelihood of benefit. Guidelines for triaging and selecting oncology patients have been developed (4), based largely on retrospective data showing poor outcomes in patients with certain prognostic factors such as increasing age (5), previous bone marrow transplantation (6, 7), evidence of neutropenia (8), the need for mechanical ventilation (9, 10) or dialysis, presence of severe sepsis (11) and progressive malignant disease (4). However, studies have shown improved outcomes in critically ill cancer patients in many of these settings, thus throwing into question the validity and reliability of these factors as prognostic tools (4, 12-20).

In one of the few prospective observational studies performed in critically ill cancer patients, Thiery et al showed that intensivists' lacked precision in selecting appropriate cancer and haematology patients for admission to ICU (21). Of the 206 patients considered for ICU

admission, approximately half were declined for being inappropriate admissions, either because they were too well or too sick to benefit from ICU. The 30-day survival of patients deemed "too well" for ICU admission was 79%, while for patients "too sick" for ICU admission it was still 26%. The investigators argued the need for a broader ICU admission policy to prevent exclusion of patients that might benefit. They proposed that a trial in ICU may be warranted in most patients not in the palliative phase of their malignancy, with a view to reassessing after several days of optimal support to reduce the chance that any patient might be denied life-prolonging treatment.

A number of predictive scoring systems have been developed including: the Acute Physiologic and Chronic Health Evaluation (APACHE) system, Simplified Acute Physiologic Score (SAPS), Mortality Prediction Model (MPM) and Sequential Organ Failure Assessment (SOFA) score (22). These scores have been validated in general ICU patients although the APACHE II has also been validated in cancer patients (23, 24).

These tools are useful for categorising the severity of the acute illness and allow comparison across ICUs, but are not intended to be used as individual patient prediction models for hospital outcomes.

Data regarding outcomes in patients with haematological and solid tumour malignancies admitted to ICU come from large specialised cancer centres, mostly from Europe or North America or from general tertiary referral hospitals or community hospitals. Most of these data are retrospective although prospective studies looking at survival rates and prognostic factors in patients admitted to ICU with haematologic malignancies have been performed (25). Comparing results between studies and extrapolating them to local clinical practice is difficult due to different approaches and philosophies on selection for ICU admission, as well

as variability in available resources and experience managing critically ill cancer patients. There are very limited data published on ICU outcomes of cancer patients in the Australian setting. Moran et al reviewed outcome data over a 10-year period from an Australian tertiary referral hospital ICU and found ICU and 30-day survival rates of 61% and 46% respectively, with survival rates improving over the period of study between 1989 and 1999 (26). Comorbidities, time to ICU admission and mechanical ventilation all correlated with survival.

Aim:

The aim of this study was to document both short and long-term outcomes for patients with haematological or solid tumours, non-electively admitted, to an Australian tertiary referral hospital ICU and explore potential prognostic factors.

Methods:

This retrospective study included all patients with haematological or solid organ malignancies non-electively admitted to the ICU at TCH from January 2008 to December 2012. Patients admitted more than once to the ICU during this period were analysed using their first admission only. TCH is a 627-bed tertiary referral hospital, with a 22-bed general medical/surgical ICU. The Haematology unit cares for patients with all forms of adult haematological malignancies and performs autograft but not allogeneic transplants, while the Medical Oncology unit cares for adult patients with all forms of solid malignancies and some lymphomas. Patients who were admitted to ICU, for post-operative recovery were excluded.

The following data were abstracted from the medical file and/or ICU database: patient demographics, malignant diagnosis, stage of disease for solid tumours, cancer treatment at time of ICU admission (i.e. curative or palliative), co-morbidities, reasons for ICU admission,

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number of organs failing at time of ICU admission and major treatments, such as vasopressor support, invasive and non-invasive ventilation, received in ICU. The co-morbidities selected included: ischaemic heart disease, chronic obstructive pulmonary disease (COPD), congestive cardiac failure (CCF), hypertension and diabetes. They were chosen based on their frequency in the general population and were not intended to be complete. Data on Eastern Cooperative Oncology Group (ECOG) performance status, other co-morbidities and their severity were not included as complete data was not available.

We defined palliative treatment as treatment where there no expectation of cure. Sepsis and multiple organ failure were defined according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (27). Sepsis was defined as a clinical syndrome characterised by the presence of both infection and a systemic inflammatory response, and multiple organ failure as the development of progressive physiologic dysfunction in two or more organ systems after an acute threat to systemic homeostasis. Respiratory distress was defined clinically as tachypnoea with use of accessory respiratory muscles or respiratory muscle exhaustion, arterial oxygen saturation lower than 90% on room air, pulmonary infiltrates, and a need for high concentration oxygen or for invasive or non-invasive ventilation [14]. Patients with hypotension or those in shock from any cause were defined as patients that required vasopressor treatment, decided by the intensivist in charge of the patient.

The APACHE II score is a severity-of-disease classification system based on twelve routine physiological measurements and other factors such as previous health status and age (28). It is scored between 0 and 71, using the most deranged value during the initial 24 hours after

ICU admission (6). A higher score corresponds to more severe disease and higher risk of death.

Patient outcomes including ICU and in-hospital mortality rate, survival at 30-days, three, six and twelve months, as well as overall survival were all calculated. Mortality outcomes, post hospital discharge, were obtained through individual departmental records, which keep an accurate record of mortality. Kaplan-Meier estimates of post-ICU survival were calculated separately for the two patients groups. Survival curves for the two groups were compared using a log-rank test. Predictors of 30-day survival such as age, primary diagnosis, stage (solid tumours), APACHE II score, reasons for ICU admission, treatment in ICU and multi-organ failure (MOF) were evaluated using univariate logistic regression. Multivariate logistic regression analysis was used to explore the independent predictors of 30-day survival. P-values less than 0.05 were considered to be statistically significant. All analyses were carried out using SPSS version 22.

Approval for the study was obtained from the ACT Health Directorate Human Research Ethics Committee (Reference no ETHLR.13.016) and the requirement for informed consent was waived as the study did not involve an intervention and there was no breach of privacy or anonymity.

Results:

During the study period a total of 3980 medical (non-surgical) patients were non-electively admitted to the ICU, of which 205 patients (5%) were oncology/haematology patients (Table

1). The number of medical patients had almost doubled over this 5 year period, from 564 in 2008 to 1034 admissions in 2012, with the proportion of oncology/haematology patients remaining relatively stable rising from 24 (4%) to 58 (6%).

Of the 205 patients admitted, 113 patients (55%) had haematological malignancies and 92 patients (45%) had solid organ malignancies. The mean age of patients was 60.3 years, and they were predominantly male (58%). The most frequent primary sites of solid tumours were lung 21 (23%), breast 17 (18%), colorectal 16 (17%), and upper gastrointestinal tract 8 (9%). The most frequent haematologic malignancies were acute leukaemia 34 (30%), non-Hodgkin's lymphoma 23 (20%), multiple myeloma 21 (19%) and Hodgkin's lymphoma 20(18%). The main reasons for ICU admission were sepsis (59%), respiratory distress (37%) and hypotension/shock (18%), with the mean length of stay in ICU 4 days ± 5.2 days (Table 2).

Of the solid organ malignancies, 82% of patients had metastatic disease, with 55% receiving palliative chemotherapy at the time of admission to ICU. Patients with haematological malignancies were more likely to receive chemotherapy with a curative intent than patients with solid organ malignancies (36% versus 17%). The mean APACHE II score in our study was 20.1.

The overall ICU survival rate for the two groups was 76%, with 128 (62%) patients alive at 30 days post-ICU admission. The median survival time was 113 days for haematological patients versus 50 days in patients with solid organ malignancies, with overall survival better for haematological patients (p=0.025), (Table 3 and Figure 1). On univariate analysis, risk factors negatively affecting 30-day survival in our study included APACHE II score, number

of failing organs and sepsis (Table 4). APACHE II score and number of failing organs remained independently statistically significant explanatory variables when combined in a multivariate logistic regression model. Patients receiving only monitoring and supportive care had a better 30-day mortality rate, likely reflecting a subgroup of less acutely unwell patients. Age, tumour type, and use of invasive or non-invasive ventilation did not impact on 30-day survival (Table 4). Logistic regression analysis indicated that number of co-morbidities did not correlate with a decreased 30-day survival.

Discussion

The ICU- survival rate of 76% and 30-day survival rate of 62%, as seen in this study, is consistent with other contemporary studies from a general hospital setting (26, 28, 29) and better than that seen in older studies (7, 30). Although these results confirm a high mortality rate for critically ill patients with malignancy admitted to ICU in an Australian tertiary hospital setting, they demonstrate that ICU admission is not universally futile and some patients do experience acceptable outcomes. It is noteworthy that 35% of patients were still alive 12 months after ICU admission, which was consistent with other studies (14, 16).

Co-morbidities have been shown to influence the prognosis, risk of complications and response to chemotherapy in patients with malignancy (9) but available data about the impact of co-morbidities on the prognosis of critically-ill patients with cancer are scant. A single prospective cohort study showed 50% of the cancer patients admitted to ICU had associated severe co-morbidities evaluated by the adult co-morbidity evaluation (ACE-27), this was shown to be independently associated with six-month mortality (10). Although our assessment of co-morbidities was limited by the retrospective nature of the data we did not find that an increasing number of co-morbidities impacted on short-term outcome.

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Existing reports suggest that cancer-specific characteristics, such as response to chemotherapy, stage of the malignancy, including long-term prognosis of the cancer have little or no impact on short-term survival during an acute critical illness (29). The poor prognosis of patients with haematological malignances who require ICU admission has been well documented, with global hospital mortality rates of 45 to 55% (11, 13), increasing to 72% when invasive ventilation is required (14). However, these patients are also more likely to receive more intensified chemotherapy protocols with a curative intent than patients with solid organ malignancy. We were not able to directly compare the relative proportion of patients in the two groups receiving "palliative" versus "curative" treatment at the time of admission to ICU, as the definition of such treatment is more complex and variable in the haematological population and was not clear on retrospective review of the data.

In a series of patients with haematological malignancies, Massion et al evaluated the ICU- and in-hospital prognosis of patients according to their long term prognosis (8). Neither ICU- nor in-hospital prognosis was correlated with long-term prognosis, but there was a strong association between short-term prognosis and acute organ dysfunction. The mean APACHE II score in our study fell within the range of 18-32 seen in other studies including haematology/oncology patients from a general hospital setting (23, 26, 29-31). As with others, our study also confirmed a significant association between APACHE II score and 30-day survival.

In our study patients with haematological cancers appeared more severely ill, with higher APACHE II scores, longer ICU admission days and longer hospital stay following an ICU admission than the solid tumour patients. However, interestingly, their short-term survival

(ICU, hospital and 30-day) was not statistically different to solid tumour patients. Their

longer-term survival (3 months+) was better (p = 0.025), likely reflecting the different

biology of the underlying malignancies.

Invasive ventilation has been shown to correlate with worse survival outcomes in several

studies, including the other Australian study reported by Moran et al (11, 12, 19, 20, 25, 26).

Interestingly our study did not demonstrate a reduced 30-day survival with either invasive or

non-invasive ventilation. The reason for this discrepancy is not clear. In our study, a lower

percentage of patients received invasive ventilation (23% compared with 46% in Moran et

al), however 35% of patients received non-invasive ventilation, which was not documented in

the Moran paper. Non-invasive ventilation has increasingly been used to avoid the need for

invasive ventilation and it is unclear if this may have affected outcome.

Morans' study is the only other published Australian study to examine outcomes for

haematology/oncology patients admitted to a tertiary referral hospital ICU in the last 20

years. Although comparisons between these two studies are difficult, due to potential

differences in approach to patient selection, resources and experience, not to mention

improvements in critical care management over the more than a decade between completion

of the two studies, it is worth reflecting on the patient factors and outcomes in the two

studies. Compared with our study, patients in the Moran study were more likely to have a

haematological malignancy (73% vs. 55%), were younger (mean age 54 vs. 60 years), with

higher APACHE II scores (28 vs. 20) and higher rates of mechanical ventilation (46% vs.

23%). Short-term outcomes in terms of ICU and 30-day survival rates were worse in the

Moran study (61% vs. 76% and 46% vs. 62%, respectively). We can only postulate that the

differences in patient factors may reflect a possible change in attitude to patient selection,

with the recognition that factors such as age, malignant diagnosis and stage do not impact on short term outcome in the setting of the acutely deteriorating patient with malignancy. Moran's study showed an improvement in outcome over the 10 year study period of their study (up to 1999), it is feasible that the better outcomes in our study support this observation.

Due to the retrospective nature of this single centre study it has several limitations. Firstly, we were not able to collect data on the method of patient selection for ICU admission as this is not standardised or necessarily well documented. We reviewed only patients that were admitted to ICU so no details on those patients that were considered but declined, or those in whom a decision to limit therapy and not refer to ICU, were available for comparison. The patient population in this study would be expected to have better survival outcomes than those declined an ICU admission, as their acceptance to ICU was very likely predicated on the intensivists' assessment that the cause for acute deterioration was potentially reversible. We were also unable to collect complete data on several patient factors such as ECOG performance status and details of all co-morbidities and their severity due to limited documentation. The main strength of this study is the long term follow up and to our knowledge, this is a first Australian study examining outcomes of critically ill cancer patients, with survival data beyond hospital discharge.

As mentioned the short-term outcomes of critically ill cancer patients admitted to the ICU in contemporary studies, including our own, is better than previously reported (4, 12), with in-hospital mortality rates not higher than critically ill patients with other primary conditions such as heart failure, liver cirrhosis or other chronic diseases (32). Possible reasons for this

include improved patient selection and earlier admission to the ICU as well as improved

diagnostic and therapeutic strategies (4, 17, 33).

Our data suggest that patients with haematological or solid tumours admitted to an Australian

tertiary hospital ICU for management of an acute clinical deterioration may achieve outcomes

that could be regarded as worthwhile and equivalent to other patients with chronic diseases.

Short term survival in this cohort was dependent on APACHE II score, underlying sepsis and

number of failing organs at time of admission to the ICU, while long term survival was likely

dependant on characteristics of the underlying malignancy. Current data does not support

any absolute criteria for triaging, and the decision to admit a cancer patient to the ICU should

be made with input from both the haematologist/oncologist and the intensivist involved in the

patients care. Further work is needed in order to find valid prognostic tools that can assist

with decision-making and patient selection for ICU admission. With short and long term

survival rates improving in cancer patients, cancer should not be seen as an exclusion criteria

ICU admission. Beyond survival outcomes, it is also important the quality of life of these

patients is assessed in future studies prospectively so that a more complete measure of benefit

is obtained.

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