Mortality within 30 days of systemic anticancer therapy at a tertiary cancer centre: assessing the safety and quality of clinical care

Michelle Wilson, Weng Mak, Melissa Firth, Sanjeev Deva, Michael Findlay

ABSTRACT

AIMS: Thirty-day mortality has been proposed to be a useful indicator of avoidable harm to patients from systemic anticancer therapies (SACT). As a quality assurance tool, we assessed the 30-day mortality rate at Auckland City Hospital and compared this with international standards.

METHODS: Clinical characteristics and treatment details of medical oncology patients who died within 30 days of SACT from October 2014–September 2015 were collected and compared with data from a similar series performed from October 2008–September 2009. SACT was limited to chemotherapy or biologic agents.

RESULTS: From October 2014–September 2015, 1,965 patients received 2,145 treatment regimens. Forty-seven patients (2.2%) died within 30 days of SACT. Treatment was given with palliative intent in 42 patients (89%) and curative intent in five (11%). Mortality rates did not change with time (2.8% in 2009 vs 2.2% in 2015). Of the patients who died within 30 days, ECOG performance status at the time of chemotherapy was one in 16 patients (34.0%), two in nine patients (19.1%) and 3/4 in nine of the 47 patients (19.1%). All patients treated with curative intent had a PS of 0 or 1. Most patients who died within 30 days were on first- or second-line therapy (45 and 38% respectively). Two-thirds of patients with a PS of 3/4 were receiving first-line therapy. Approximately half the patients died during their first cycle of therapy (48.9%).

CONCLUSIONS: Our local 30-day mortality data compares favourably to international benchmarks of 5% and has not increased over time. Performance of similar studies locally and nationally should be undertaken to continue to assess and improve the quality of our patient care.

The expertise of an oncologist reflects his/her knowledge of chemotherapy and ability to individualise this to the patient under their care. Over the past 30 years there has been an increase in both the number of chemotherapy agents and additionally the indications for treatment.1,2 In 2016, 45 new drugs were approved by the Food and Drug Administration (FDA) with 15 of these for the treatment of cancer.2 There are now over 100 drugs approved for use in oncology with many of these recommended for multiple indications. These treatments are given with the aim of allowing patients to live longer and better, but they also have the potential to contribute to patient morbidity.1 The risk of harm is amplified when prognosis is poor and time is short.

There is a paucity of relevant information on the clinical benefit/harms of treatments as the patient reaches end-of-life, and the decision to continue chemotherapy in this setting is a complex one, involving patient, physician and societal beliefs. With recognition of the importance of high quality end-of-life care, the spotlight has now turned to chemotherapy to evaluate what value it provides during this time. In patients with advanced non-small cell lung cancer, early palliative care has been
associated with improved quality of life, less aggressive medical care and importantly an improved median overall survival.5

With the mandate of ensuring the safe delivery of health care to its constituents and growing concerns that end-of-life chemotherapy was leading to a “bad death”, the National Confidential Enquiry into Peri-Operative Deaths (NCEPOD) in the UK undertook a nationwide audit to review all cases of death within 30 days of chemotherapy administration.6 During a two-month period, 47,050 chemotherapy doses were given with 1,044 deaths observed. The case notes and follow-up questionnaires of a subset (478 of 1,044) of the patients were reviewed by a panel of oncologists, nurses, pharmacists and patient advocates.6 In the advisors’ opinion there was room for improvement for care in 49% of the patients, with care reported to be well below an acceptable standard in 8%.6

The 30-day mortality rate provides a technically feasible approach to rapidly identify a cohort of patients that oncologists can look back on and learn from.7 This has been investigated at many institutions since then, with mortality rates varying from 3.1–12.3%.8–12 With the increasing importance of clinical governance and the rising cost of chemotherapeutic-based health care, we looked to investigate the 30-day post-systemic therapy mortality in a large tertiary centre in New Zealand as a key performance indicator (KPI) for our oncology practice.13

Methods

This study was conducted at Auckland City Hospital. This is a regional cancer site offering medical oncology and haematology care in a centralised manner to three neighbouring district health boards, servicing a population of approximately 1.4 million people.

Local approval was achieved. Chemotherapy prescriptions and clinical notes are stored electronically at Auckland City Hospital. Cases were identified through the pharmacy records and clinic appointment records. This list was cross-referenced against New Zealand Health Information Services Mortality collection (MORT) to generate a list for case finding. This was also compared to hospital clinical records and mortality documentation.

The study included all adult patients who had at least one cycle of chemotherapy from 1 October 2014 until 30 September 2015 under medical oncology at Auckland City Hospital. Patients receiving concurrent chemoradiation were included. Patients receiving treatment under haematology or treated in private practice were excluded. The definition of chemotherapy included all cytotoxic drugs and oral targeted therapies were excluded. Oral targeted therapies were excluded due to the challenges in defining the patient populations with our current databases. Cases included were those where patients died within 30 days of their last chemotherapy dose administered from 1 October 2014 until 30 September 2015.

This was compared to data collected in a similar project from 1 October 2008 until 30 September 2009 (NTX/10/05/EXP). An identical protocol was used to define eligible patient populations and determine 30-day mortality. Any patient who died within 30 days of their last dose of systemic therapy was included. This was calculated per course.

The information captured for the audit included: age, ethnicity, sex, cancer diagnosis, stage of disease, ECOG performance status,14 chemotherapy regimen, line of chemotherapy, cycle of treatment and the intent of treatment (curative vs palliative). If the performance status was not documented in the clinical notes, then this was documented retrospectively. Both prospective and retrospective documentation of performance status was performed. Performance status was a key concern as is an important prognostic tool. A score of 0 represented asymptomatic patients (fully active); 1 represented symptomatic but completely ambulatory; 2 represented symptomatic with less than 50% of the day in bed; 3 represented symptomatic with more than 50% of the day in bed; and 4 represented bedbound. A score of 5 represents death.

Curative treatment included adjuvant and neoadjuvant treatment and chemotherapy given with curative intent. Palliative chemotherapy referred to therapy given to improve symptoms and to prolong life. The cause and location of death was recorded where available. Both inpatient and outpatient notes were recorded. Data was extracted by two independent investigators to minimise bias. Cause of death,
however, was documented by one investigator. In cases where this was not clear, this was reviewed in conjunction with another investigator.

Results

1,965 patients received 2,145 courses of chemotherapy at Auckland Hospital from 1 October 2014 until 30 September 2015. Of these, 47 patients (2.2%) died within 30 days of SACT. Of these 47 patients, treatment was given with palliative intent in 42 patients (89.4%) and curative intent in five (10.6%). From October 2008 to September 2009, 43 patients (2.8%) died within 30 days of SACT. 30-day mortality data was similar across the two time periods (2.2%—2009 vs 2.8%—2015).

Across both time periods examined, the majority of patients who died were being treated with palliative intent, 51 patients (87%) in 2009 and 42 patients (89.4%) in 2015. The median age was similar at 59 years and 61 years respectively (Table 1). Of the 47 patients who died during the period of interest in 2015, 28 (59.6%) died as an inpatient in hospital, with 19 dying outside of hospital (40.4%).

The results presented below relate to the cohort of patients who died within 30 days of systemic therapy.

Performance status

The percentage of patients with performance status documented increased from 30.5% in 2009 to 78.7% in 2015. In 2015, performance status at the time of the last

Table 1: Demographics of patients dying within 30 days of therapy over the two time periods.

<table>
<thead>
<tr>
<th></th>
<th>2009 n=43 (%)</th>
<th>2015 n=47 (%)</th>
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<tbody>
<tr>
<td>Median age (range)</td>
<td>59 years (31–81 years)</td>
<td>61 years (25–83 years)</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (39.5)</td>
<td>19 (40.4)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (60.5)</td>
<td>28 (59.6)</td>
</tr>
<tr>
<td>Treatment intent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>2 (4.7)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Palliative</td>
<td>41 (95.3)</td>
<td>42 (89.4)</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (4.7)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>1</td>
<td>2 (4.7)</td>
<td>16 (34.0)</td>
</tr>
<tr>
<td>2</td>
<td>3 (7.0)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>3 or 4</td>
<td>4 (9.3)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>32 (74.4)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Type of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12 (27.9)</td>
<td>16 (34.0)</td>
</tr>
<tr>
<td>Breast</td>
<td>12 (27.9)</td>
<td>13 (27.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (9.3)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>3 (7.0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Skin</td>
<td>5 (11.6)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>0 (0.0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2 (4.7)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (11.6)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Median time from treatment to death (range)</td>
<td>14 days (0–30 days)</td>
<td>16 days (0–29 days)</td>
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</table>
cycle of chemotherapy was zero in three patients (6.4%), one in 16 patients (34.0%), two in nine patients (19.1%) and three or four in nine patients (19.1%). Performance status was not documented in 10 patients. Of those patients with a performance status of 3/4, 55.6% (five of nine patients) were treated as an inpatient. All patients treated with curative intent had a performance status of 0 or 1.

Line of therapy and cycle of treatment

Approximately half the patients during both periods were receiving first-line of therapy (62.8%—2009; 44.7%—2015) (Figure 1). In 2009, 14% had had at least three prior lines of therapy. In 2015 this was 17%. This indicates that the cohorts of patients were not heavily pre-treated. Of interest, approximately half the deaths occurred during the first cycle of treatment (53.5%—2009; 48.9%—2015) (Figure 1).

Cause and location of death of patients treated October 2014–September 2015

Of the five patients who died within 30 days of therapy who were being treated with curative intent, four were receiving first-line therapy and one second-line. Four of the patients died in cycle 1 of therapy. The remaining patient died in cycle 3. Cause of death was documented in three of the cases. In patients treated with curative intent, the majority of deaths were treatment-related

Table 2: Comparison with reported international 30-day mortality rates post-chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Auckland New Zealand</th>
<th>Ballarat Australia (Yoong et al)12</th>
<th>Royal Marsden UK (O’Brien et al)9</th>
<th>Christie UK (Khoja et al)9</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality rate</td>
<td>2.2%</td>
<td>3.4%</td>
<td>8.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>0.23%</td>
<td>0.79%</td>
<td>0.61%</td>
<td>0.44%</td>
</tr>
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</table>
Discussion

This study demonstrated a post-systemic therapy 30-day mortality rate of 2.2% in our patient population. The results of this study are remarkably similar to the national survey conducted by NCEPOD in 2008. In this study they observed a mortality rate of 2.2% per patient treated. In their survey the percentage of patients who were being treated with curative intent was 14%
(compared with 14% in this study), the number of patients who died following cycle 1 was 52% (compared with 58%) and the number of patients who were on second-line or greater chemotherapy was 45% (compared with 41%).

This study reinforces that the 30-day mortality rate is a feasible measure to assess patient outcome and represents a viable key performance indicator in this field. Limitations of this audit include its relatively small size and retrospective nature. This is confounded by insufficient and missing data, particularly relating to causality of death. In particular, it was not possible to determine the relationship between treatment and death in two patients treated with curative intent. An expanding area this series fails to address is the mortality of patients receiving targeted therapy. These represent a significant cost to the health sector, and the appropriateness of their use at this stage in a patient’s clinical course also warrants careful consideration. The results of this study, however, emphasise the need to ensure ongoing accountability in the delivery of care at our centre.

The intent of treatment is key when implementing the 30-day mortality rate as a key performance indicator. A death of a patient receiving an adjuvant/curative treatment represents a devastating loss of life. In this group the observed chemotherapy mortality rate itself should be the measuring stick. In our series, five patients receiving adjuvant therapy died within 30 days of chemotherapy, of which three deaths (60%) were documented to be related to therapy. With respect to treatment-related deaths, our rate per total deaths (10.6%) was in keeping with other series (7.5% Royal Marsden, UK, 23% Ballarat, Australia, 11% Christie, UK and 3.9% East Kent, UK), but our absolute number was low at only five. Overall, our treatment-related mortality rate was only 0.23%. These cases are now reviewed and discussed at our local mortality and morbidity meetings.

In patients receiving palliative chemotherapy, death is the outcome of an untreated progressive tumour and there is a reflex desire to “do something” to delay this. Chemotherapy, in this context, is given with the goal of palliating symptoms and prolonging life. Modern chemotherapy regimens may achieve these goals, but their inherent cytotoxic nature means that in a proportion of patients it can hasten or directly lead to death. Symptom relief is a strong motivator for undertaking treatment in patients. As evidence linking aggressive end-of-life care to worse patient outcomes continues to emerge, the use of a 30-day post-chemotherapy mortality rate should gain traction as an important quality indicator. This is of relevance not only for the treating doctors and patients themselves, but also for health care providers to ensure the efficient allocation of increasingly scarce resources. It is important that we do not allow inappropriate treatment to delay good palliative care as ultimately this will result in poor-quality care. Recognising the challenges in prescribing in this setting, we recommend discussion of these cases in our mortality meetings.

There is little clinical guidance on what the expected minimum clinical benefit for which ongoing chemotherapy is indicated, as such societal expectations and health care structure dictate to what degree and how long chemotherapy is prescribed. The paradox of maintaining hope for positive outcomes despite the diagnosis of a terminal illness results in over-optimistic physicians and patients who are willing to consider chemotherapy for small benefits. When faced with similar hypothetical scenarios, oncologists would more readily opt out of treatment. These differences may reflect the difficulty of making life-value judgements in hypothetical scenarios, but may also represent the difficulty in accurately communicating realistic outcomes of treatment.

Large geographic variation in the percentage of patients receiving palliative chemotherapy in the last month of life exists, ranging from 8% in the UK, 19% in Korea, 16–23% in Italy and 13–37% in Portugal. Reasons for the use of chemotherapy in the last month of life have been investigated and include patient-driven and family-driven factors, quality of life improvement and symptom palliation, as well as uncertainty regarding prognosis and response. The NCEPOD review emphasised the dilemmas facing clinicians’ treatment decisions, with 20% of clinicians reporting the decision to treat as difficult in
cases where patients had advanced disease and poor performance status. In all, 6% reported they would have acted differently retrospectively and 13% felt the treatment decision may have been inappropriate. We encourage the opportunity for these cases to be discussed within the smaller tumour-specific medical oncology teams as part of our peer review process.

Understanding the decision to prescribe chemotherapy particularly if the patient has a poor performance status is important. Factors such as the tumour sensitivity, predicted survival outcomes, side effects and underlying co-morbidities are relevant and need careful consideration. A recent large national series from the UK looked at rates by age, income and body mass index. We did not look into this degree of detail but their findings raise a number of key issues, particularly the impact of age on what a patient is willing to accept and a clinician willing to offer. There are substantial variations in patient attitudes when making decisions around chemotherapy. In some circumstances, the principles of chemotherapy prescribing can be overridden by patient wishes and this has the potential to be to the detriment of the patient. Cessation of chemotherapy within the last two weeks of life has been set as a benchmark for improving clinical practice in the Quality Oncology Practice Initiative (QOPI) of the American Society of Clinical Oncology. It has been estimated that the appropriate use of chemotherapy in the last two weeks of life is less than 10%. However, studies have shown that oncologists are poor at predicting survival of patients with advanced cancer. Palliative prognostic scoring tables have been advocated for guiding decisions but are complex. Accurate assessment of a patient’s performance status has been advocated as a useful alternative in daily practice. Reflecting this, advanced age and poor performance status have been identified as high-risk factors for mortality in solid tumours and lymphoma. Documentation of the performance status is therefore of key importance in oncology practice. Despite this, this is poorly done. In our initial patient cohort, performance status was only documented in 30% of patients but this improved to 70% in our latest cohort. A challenge with this is recognising the potential subjectivity with this score. The NCEPOD found that 21% of patients had a performance status of greater than 2. In our latest cohort, nine patients, six (66%) were receiving first-line therapy. Oncologists need to be cognisant that the estimated treatment benefits may not be accurate when the patient would have not met the inclusion criteria for the study of interest. Additionally, the American Society of Clinical Oncology (ASCO) guidelines specifically recommend against the use of chemotherapy in solid tumour patients who have not benefited from prior therapy and who have a performance status score of 3 or more. Poor performance status is recognised to be associated with poor survival, reduced response and increased toxicity from treatment. Chemotherapy use in patients with a poor PS has not been shown to improve quality of life near death.

This audit provides a platform to review local practices and outcomes outside a clinical trial. It raises clinicians’ awareness and accountability when making treatment decisions and reinforces that careful patient selection is critical. While this key performance is specific to oncology, it highlights the importance of regular integration of

<table>
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<th>Clinical practice interventions proposed</th>
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<tr>
<td>1. Three-monthly review of 30-day mortality with cases reviewed at the local mortality and morbidity meeting</td>
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<tr>
<td>2. Consideration of palliative chemotherapy in borderline performance status patients (&gt;2) needs to be discussed within the specialist oncology team</td>
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<tr>
<td>3. Performance status should be documented at the time of assessment</td>
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<tr>
<td>4. The role of the specialist nurse as a patient contact is critical</td>
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</table>

Table 3: Clinical practice interventions proposed.
KPIs in clinical practice to ensure quality care and accountability for our patients. Based on the results of this study, four interventions have been proposed (Table 3).

**Conclusion**

This study demonstrates our mortality rates are in keeping with international standards. This quality assurance initiative has allowed us to introduce recommendations to continue to raise the quality of patient care at our centre. There are no national benchmarks for what is an acceptable post-chemotherapy 30-day mortality rate, but we propose our results represent an initial step for us to build upon in practice. This highlights the value of collecting data beyond clinical trials to better understand the patients managed in our daily practice.

**Competing interests:**

Dr Wilson reports travel support from MSD and Roche. Dr Deva reports travel support from Roche.

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**URL:**


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