



Reflecting on inpatient palliative chemotherapy— is there ever a “right place” at the “right time”?

D. Rayson MD and D.A. Kain MA MD†*

Early in clinical training, medical oncologists are taught that the goals of any palliative oncologic therapy include symptom control, quality-of-life improvement through disease stabilization, and prolongation of progression-free survival. Ideally, achieving those goals translates into an overall survival benefit, as has been observed in two pivotal clinical trials with symptom-directed primary endpoints—although that benefit is more the exception than the rule^{1,2}. Lying in wait to disrupt those goals, treatment-induced toxicities can quickly scramble the clinical benefit equation and lead to exponentially more symptoms that have to be controlled, a prolongation and deepening of malignancy-related suffering, the loss of functional independence, and a shorter-than-expected overall survival. The spectrum of treatment-induced toxicity ranges from the predictable, slowly cumulative, and management-responsive, to the acute, idiosyncratic, and tsunami-like, and they are the subject of morbidity and mortality rounds in all oncology training programs.

Predicting palliative clinical benefit from systemic therapy is an imprecise art. Efforts to develop a scientific framework upon which to base decision-making date to 1949, with the publication of what would become eponymously known as the Karnofsky performance status (KPS). Initially conceived as a tool to enable assessment and documentation of assistance needs and physical function for patients with cancer, it was published as a chapter titled “The Clinical Evaluation of Chemotherapeutic Agents” in a book titled *Evaluation of Chemotherapeutic Agents*. It was therefore inevitably linked to the evaluation of the clinical and functional impact of chemotherapy³.

It is a testament to the robustness of the KPS that, despite being developed in an era when nitrogen mustard, urethane, and Fowler’s solution were the only members of a club of chemotherapy agents perceived as having clinical value, the tool remains, together with its simpler, younger cousin, the Eastern Cooperative Oncology Group performance status (ECOG PS)^{4,5}, a standard metric for chemotherapy decision-making.

Inclusion criteria for all clinical trials examining novel systemic therapies specify assessment of either the KPS or the ECOG PS, and both measures are routinely included in clinical and funding guidelines pertaining to the selection of patients appropriate for palliative cancer therapies, thus enshrining their relevance and importance within two essential cancer treatment spheres: discovery and access.

Individuals requiring hospitalization along their disease trajectory represent a considerable fraction of the adult patient population with incurable solid tumours. In general, three broad phases during which hospitalization might be required can be conceptualized: at diagnosis, during receipt of active cancer therapy, and at end-of-life. Many patients will never require hospitalization; others will be admitted one or multiple times because of their disease, the secondary complications of their disease, treatment intensity, treatment-induced toxicities, symptom crises, situational chaos and caregiver burnout, or requirement for end-of-life care.

Practitioners are taught that hospitalization implies a maximal KPS of 40 (“disabled; requires special care and assistance”) or an ECOG PS of 3 (“capable of only limited self care, confined to bed or chair more than 50% of waking hours”). Such patients are typically excluded from clinical trials because of expectations of minimal benefit and considerable harm. Hospitalization is also a key factor in determining treatment options in non-trial care and is sometimes used as a dichotomous variable simplifying the cancer treatment decision-making process—as in, “sick enough to be in hospital = too sick to benefit from systemic therapy.” In many instances, that understanding is in the best interest of patients and adheres to the Hippocratic Oath of *primum non nocere*.

Wheatley–Price *et al.*⁶ examine survival outcomes and the proportions of patients well enough for discharge home and for receiving further (presumably outpatient) chemotherapy in a convenience cohort of 199 hospitalized patients receiving palliative

chemotherapy as inpatients during a 21-month period at The Ottawa Hospital Cancer Centre. Most of the patients were admitted because of disease-related symptoms, received first-line chemotherapy, and had a diagnosis of either lung cancer (22% small-cell, 16% non-small-cell) or breast cancer (23%). Key limitations of the study, recognized by the authors, included a criterion excluding patients who received non-cytotoxic systemic therapy (thereby limiting the understanding of the spectrum of outcomes associated with the range of cancer treatment options currently available) and also the fact that ECOG PS was not routinely charted (coupled with an assumption that, given the fact of hospitalization, it had to be 2 or greater). The goals of inpatient chemotherapy were not described, and the analysis was limited by the small and heterogeneous patient population.

Despite modest conclusions, the work by Wheatley–Price *et al.* provides an important “real-world” framework that should stimulate more active investigation of the potential benefit—and harms—of palliative therapy administration during hospitalization. Although decisions about novel noncytotoxic therapy for this patient population are less controversial, clinical trials involving targeted therapies use the same measures of performance status as key inclusion criteria, and the treatments themselves can be associated with toxicities that affect quality of life and functional status. Although an “easier” decision, the impact of palliative noncytotoxic systemic therapy for individuals with a poor PS, assumed by the surrogate of hospitalization, is an important clinical question awaiting data.

Clinical endpoints in the Wheatley–Price study deemed to reflect positive outcomes included discharge from hospital and the ability to receive further chemotherapy. Those assumptions deserve some reflection and raise the question of whether “quality of life” can be achieved only outside a hospital. The “quality of life” concept carries a great deal of individual variation in its definition. For some, it implies mobility and a high degree of function; for others, it is about having pain and other distressing symptoms well controlled; and for still others, quality of life is about being able to spend meaningful time with loved ones. The latter two can most certainly take place within a hospital or hospice setting, and often do when practical considerations do not allow for a patient to be discharged. Future studies examining the benefit from palliative systemic therapy should ideally incorporate meaningful quality-of-life clinical endpoints rather than make inferences based on hospital admission status.

There are limitations to an isolated assessment of PS within the context of spiralling symptomatology. Patients might enter hospital with a PS of 3 that improves to 1 a few days after admission. The PS “response” to timely and effective symptomatic and supportive care might shift the risk–benefit equation

for those with modifiable symptoms. Such a shift might be particularly true in the era of increasingly targeted therapy for advanced malignancy. If so, ongoing efforts to integrate expertise in symptomatic and supportive care with early involvement of the palliative care team could be important. For those receiving palliative chemotherapy in hospital, is there an ideal place *within the hospital* to optimize outcomes? Would it matter if a patient were on an inpatient oncology unit compared with an inpatient palliative care unit? Further study of this particular issue could result in patient-centered changes to current practice.

The divide between “active” cancer treatment and “palliative” care was relatively straightforward in an era when chemotherapy was unavoidably toxic and expertise in symptom control was in its infancy. Importantly, recent research supports the practice of integrating early referral of oncology patients to palliative (and supportive) cancer care programs rather than depicting those two disciplines as sequential points in the journey of the patient with metastatic disease. Recent trials demonstrate improved quality—and in some instances quantity—of life in patients referred early to palliative care practitioners^{7,8}.

Illustrating that evolution, a 2006 consensus report from the American Society of Clinical Oncology and the European Society for Medical Oncology emphasized the apparent solitudes by stating that “when effective cancer therapy is no longer available, patients should have access to optimal palliative care and counseling with respect to end of life issues,” thus emphasizing the notion that palliative care involvement is required only when options for “effective cancer therapy” are exhausted^{9,10}. In 2012, based on results from a phase III clinical trial of early palliative care involvement for those with metastatic non-small-cell lung cancer, a provisional clinical opinion from the American Society of Clinical Oncology stated that individuals with metastatic non-small-cell lung cancer should be offered “concurrent palliative care and standard oncologic care at initial diagnosis”¹¹. The times are indeed a-changing.

As always, the real world differs significantly from the patient population meeting inclusion criteria for a clinical trial. The real world is filled with unrealistic expectations, patient and familial desperation, unresolved aspirations, and reflexive hope that things will get better. As clinicians, we deal with those issues in the context of an oath handed down to us from antiquity and of an assessment tool originating during the earliest moments of cancer treatment. Data such as those presented by Wheatley–Price *et al.* should remind us that, despite the exponential advances in our understanding of the molecular biology of malignancy, when the goal of therapy is palliative, we need all the help we can get in making the right decision for the patient in front of us.

CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

REFERENCES

1. Tannock IF, Osoba D, Stockler MR, *et al.* Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756–64.
2. Burris HA 3rd, Moore MJ, Andersen J, *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas trial: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
3. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, ed: *Evaluation of Chemotherapeutic Agents*. New York, NY: Columbia University Press; 1949: 199–205.
4. Karnofsky DA. Chemotherapy of neoplastic disease: agents of clinical value. *N Engl J Med* 1948;239:299–305.
5. Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
6. Wheatley-Price P, Ali M, Balchin K, Spencer J, Fitzgibbon E, Cripps C. The role of palliative chemotherapy in hospitalized patients. *Curr Oncol* 2014;21:187–192.
7. Temel JS, Greer JA, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733–42.
8. Zimmermann C, Swami N, Krzyzanowska M, *et al.* Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014;383:1721–30.
9. ASCO–ESMO consensus statement on quality cancer care. *J Clin Oncol* 2006;24:3498–9.
10. Rayson D, McIntyre P. Transitions to palliation: two solitudes or inevitable integration? *Curr Oncol Rep* 2007;9:285–9.
11. Smith TJ, Temin S, Alesi ER, *et al.* American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol* 2012;30:880–7.

Correspondence to: Daniel Rayson, Division of Medical Oncology, Room 460, Bethune Building, 1276 South Park Street, Halifax, Nova Scotia B3H 2Y9.

E-mail: daniel.rayson@cdha.nshealth.ca

* Division of Medical Oncology and Atlantic Clinical Cancer Research Unit, QEII Health Sciences Centre, Dalhousie University, Halifax, NS.

† Division of Palliative Medicine, QEII Health Sciences Centre, Dalhousie University, Halifax, NS.