Supportive care and palliative care: a time for unity in diversity

This issue of *Annals of Oncology* highlights a number of articles that deal with topics related to the supportive and palliative care of cancer patients. What is the difference between these two aspects of patient care? Where does ‘palliation’ end or ‘support’ start? This has been an area of debate for a long time, but as in all subspecialties of oncology, one has to realize that there is a continuum. Today’s management of patients with cancer is of a multidisciplinary nature, a fact exemplified by the bi-annual European Multidisciplinary Cancer Care Conference. Historical reasons have led to the development of specialist groups that have dedicated their expertise more towards issues frequent at the end of life (often called palliative care) or more towards issues around treatment management and post-treatment issues (supportive care). According to the Multinational Association for Supportive Care in Cancer, supportive care is the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side-effects across the continuum of the cancer experience from diagnosis through anticancer treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship and end-of-life care are integral to supportive care. Supportive care alleviates symptoms and complications of cancer, reduces or prevents toxic effects of treatment, supports communication with patients about their disease and prognosis, allows patients to tolerate and benefit from active therapy more easily, eases emotional burden of patients and caregivers, helps cancer survivors with psychological and social problems [1].

The European Society for Medical Oncology (ESMO) has recognized the importance of these approaches for a long time, and one of its key programs is its designated centers of Integrated Oncology and Palliative Care. Any oncology department or cancer center can apply: size is not important; to be eligible what matters are the quality and the extent of the integration of services. The criteria for accreditation are based on recommendations of the World Health Organization guidelines on the provision of palliative care for patients with cancer, and reflect the issues of integration, credentialing, service provision, research and education. The main objectives of the program are promoting the integration of palliative care services into the existing national cancer care guidelines, encouraging palliative care education and training for medical oncologists as well as other healthcare professionals, expanding the cooperation between ESMO and other existing professional medical associations and organizations worldwide in supporting and sustaining palliative care development [2].

Further, ESMO has dedicated its 2011 handbook to Nutrition and Cancer [3], and as a final reference to ESMO’s recognition of the area of supportive and palliative care one should mention the various ESMO clinical practice guidelines [4], which are intended to provide the user with a set of recommendations for the best standards of cancer care, based on the findings of evidence-based medicine. There are presently nine guidelines for supportive and palliative care, and


Reports of tumor registry studies need to have clear clinical relevance; pre-submission queries are encouraged.

The journal remains committed to translational research for the development of oncology [2], including basic, i.e. wholly preclinical, cancer research where clinical potential is clear.

**letters to the editor**

Letters to the editor are for correspondence relating to previously published articles, and only then within an appropriate time frame (not later than 2 years after publication), or interesting practice points, e.g. emerging side-effects of new drugs, rare diseases where there is a real practice issue.

Case reports will no longer be considered for publication as Letters to the editor.

**editorials**

The submission of an editorial remains by invitation only.

I hope that these remarks are clear in both statement and intent. It is not my wish to discourage anyone with good work from sending it to *Annals of Oncology*. Rather by being honest about what we can and will consider I hope to give back time to authors, editors and referees and so encourage the best forms of engagement from all with the journal.

I think it is clear that *Annals* is an increasingly popular destination for the best in oncology research; long may it remain so.

J. B. Vermorken
Editor-in-Chief
And the Associate Editor Team

**references**

the one on prevention of nausea and vomiting is a nice example of collaboration with a society specifically dedicated to supportive care [5].

The word used to designate this activity is not trivial. Obviously translations in various languages and cultures render the discussion even more complex [6], but for several years there has been a negative perception of palliation, as if it was synonymous with patient abandonment by the ‘active’ treatment team. As indicated above, the reality is that supportive and palliative and ‘active’ are a continuum where each has a role to play at a particular moment of the patient’s itinerary. In 2009, colleagues from the MD Anderson Cancer Center discussed that referrals to palliative care tended to occur late in the trajectory of illness [7]. It was hypothesized that the perceived association between the name palliative care and hospice was a barrier to early patients’ referral. They conducted a survey among a random sample of 100 medical oncologists and 100 midlevel providers from The University of Texas MD Anderson Cancer Center. A total of 140 of 200 (70%) participants responded (74 midlevel providers and 66 medical oncologists). More participants preferred the name supportive care (80%, 57%) compared with palliative care (27%, 19% P < 0.0001). Medical oncologists and midlevel providers stated increased likelihood to refer patients on active primary (79% versus 45%, P < 0.0001) and advanced cancer (89% versus 69%, P < 0.0001) treatments to a service-named supportive care.

The name palliative care compared with supportive care was perceived more frequently by medical oncologists and midlevel providers as a barrier to referral (23% versus 6% P < 0.0001), decreasing hope (44 vs 11% P < 0.0001) and causing distress (33% versus 3% P < 0.0001) to patients and their families. Medical oncologists and midlevel providers much more preferred the name supportive care and stated more likelihood to refer patients on active primary and advanced cancer treatments to a service-named supportive care.

As a follow-up to this study, the team changed the name of the unit. The result was remarkable. In a study of records of 4701 consecutive patients with a first palliative care consultation before and after the name change they found: (i) a 41% greater number of palliative care consultations (1950 versus 2751 patients; P < 0.0001), mainly as a result of a rise in inpatient referrals (733 versus 1451 patients; P < 0.0001), and (ii) in the outpatient setting, a shorter duration from hospital registration to palliative care consultation (median, 9.2 months versus 13.2 months; hazard ratio (HR), 0.85; P < 0.001) and from advanced cancer diagnosis to palliative care consultation (5.2 months versus 6.9 months; HR, 0.82; P < 0.001), and a longer overall survival duration from palliative care consultation (median 6.2 months versus 4.7 months; HR, 1.21; P < 0.001) [8]. The name change to supportive care was thus associated with more inpatient referrals and earlier referrals in the outpatient setting. The outpatient setting facilitated earlier access to supportive/palliative care and we can agree with the authors that it should be established in more centers.

In line with this observation, this issue of Annals of Oncology carries a study that reports on the positive impact of early access to a palliative/supportive care intervention on pain management in patients with cancer [9]. This is a multicenter cross-sectional study carried out in 32 Italian hospitals including 1450 patients receiving analgesic therapy for cancer pain. Statistically significant differences in the analgesic drug administration according to the care model were found: non-opioids were more frequently used in a standard care (SC) setting (9.5% versus 2%; P < 0.001), while strong opioids were introduced more frequently in the early access to a palliative/supportive care (ePSC) group (80% versus 63%; P < 0.001). The number of patients with severe pain was lower in the ePSC group compared with the SC group (31% versus 17%; P < 0.001).

One has to finally mention the recent interest in palliative care as a means to support patients and have an impact on survival, an interest sparked by the publication of a study evaluating patients with advanced non-small-cell lung cancer, which reported that early palliative care in these patients improves the quality of life, mood, and survival despite less aggressive end-of-life care compared with standard oncology care alone [10].

The American Society of Clinical Oncology (ASCO) is to be commended for having published a provisional clinical opinion on the topic [11]. This balanced review of the available evidence (seven randomized, controlled trials) demonstrating the benefits of palliative care in patients with metastatic cancer who are also receiving standard oncology care concludes that survival benefit from early involvement of palliative care has not yet been demonstrated in other oncology settings but substantial evidence demonstrates that palliative care—when combined with standard cancer care or as the main focus of care—leads to better outcomes in patients and caregivers. Therefore, it was the ASCO panel’s expert consensus that combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.

However, as mentioned by the ASCO committee, ESMO had already stated in 2003 [12] that ‘since most cancer patients receive their cancer care in dedicated clinics or hospitals, it is imperative that these facilities provide an adequate supportive and palliative care infrastructure as part of the global service. Key tasks of supportive and palliative care provision in the cancer center include the screening of cancer patients to identify patients with specific needs, and the provision of real-time supportive and palliative care interventions as part of routine cancer care.’ This was already a call for unity in diversity.

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references
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Learning from toxicity patterns in phase I trials during the era of mechanism targeted agents

In this month’s journal are companion papers describing observed toxicity in patients entering on phase I trials within the Royal Marsden Hospital (RMH), UK, and the MD Anderson Cancer Centre, USA (two of the biggest drug development units in the world) [1, 2]. These studies assessed patients enrolled in the period of 2005-2009 where oncology drug development has concentrated on molecular targeted agents (MTAs). What lessons can we learn from these studies to help us improve the care of patients on phase I studies?

A major ethical issue encountered while discussing entry to phase I trials is the risk of exposing patients to toxicity, when historical response rates to therapies in phase I studies are low [3–5]. Identification of patients who are at greater risk of toxicity or have less chance of response is important to enable informed discussion with a patient about the risk: benefit ratio of entering on a phase I study. Physicians often informally try to assess the risk of a patient going on to suffer from unacceptable toxicity before entry on a phase I study, but the criteria they use vary and have little or no evidence base [6].

The two studies reported here retrospectively analyse toxicity rates and risk factors in populations treated on phase I studies. There are minor differences between the studies; in particular, Molife et al. [1] from the Royal Marsden excluded patients receiving conventional cytotoxics from their analysis, while Wheler et al. [2] from the MD Anderson included patients who received cytotoxics (379 of 1181 patients in their cohort, of which 215 patients received a cytotoxic in combination with a targeted agent). However, both series reported similar grade 3 and 4 toxicity rates of 16% and 10.3%, respectively, with a possible drug-related death rate of 0.4% in both studies [1, 2].

There is remarkable consistency in rates of toxicity and death between these studies and previous reports of toxic effects within phase I studies [1, 2, 5, 7], although some smaller series have reported higher toxicity rates of over 30% [8, 9]. This consistency in toxicity rates is seen despite the use of different agents and a move from the development of cytotoxics to the development of MTAs, although Wheler et al. [2] did find that toxicity rates were slightly higher in patients receiving cytotoxics. Interestingly, the toxicity rates reported here are lower than rates seen on later phase trials, despite the rigorous data—capture on phase I trials. This may reflect the selection of a fitter patient population for phase I studies, the probability that some patients on a phase I trial are receiving sub-therapeutic doses or a combination of these factors.

In both studies, the authors attempted to identify factors that might predict patients who are at higher risk of toxicity, and in both studies, poor performance status was determined to be associated with increased rates of severe toxicity (more than double those seen in patients with good performance status) [1, 2]. It is sometimes difficult to restrict entry on to phase I studies to patients with good performance status, particularly when an exciting new agent is under evaluation. However, these studies confirm that the risk: benefit ratio may be lower in patients with poor performance status. In addition, inclusion of patients with poor performance status in phase I protocols may lead to the observation of more dose-limiting toxicities (DLTs) and the classification of a lower dose as tolerable, with a subsequent detrimental effect on further clinical development of a new agent.

In addition, both studies showed that the RMH score (albumin < 35 g/l, LDH greater than the upper limit of normal and > 2 metastatic sites), which was designed to identify patients less likely to benefit from entry on to a phase I study in terms of response [10], did not predict subsequent toxicity. The addition of performance status (which predicts toxicity) to the RMH model does not result in any significant improvements in terms of predicting survival following entry on to a phase I trial, but poor performance status may be associated with early trial discontinuation [4]. Therefore, the studies published here can be used, in conjunction with other recent studies, to help to better inform discussions with patients about entry on phase I studies; in particular, as to the possibilities of toxicity, response and likely prognosis. This information is vital if patients are to make informed decisions about entry on to a phase I study [11].