Editorial

Palliation in metastatic non-small cell lung cancer: Early integration with standard oncological care is the key

Lung cancer remains one of the most common malignancies globally (and within India also), amongst males as well as for both gender combined.[1,2] Approximately, 80% of cases are of non-small cell lung cancer (NSCLC) histology and present with advanced/unresectable disease (stages IIIB and IV) in which traditional treatment options like chemotherapy and radiation therapy are aimed at disease and symptom control rather than at achieving a cure.[3,4] For advanced and metastatic NSCLC, the last two decades have witnessed the emergence of molecularly targeted therapy as an important addition to the therapeutic armamentarium. In particular, adenocarcinoma patients should undergo testing for the presence of sensitizing mutations in the epidermal growth factor receptor (EGFR) gene and for rearrangements in the anaplastic lymphoma kinase (ALK) gene since these are two actionable ('druggable') targets wherein use of EGFR tyrosine kinase inhibitors (EGFR-TKIs like gefitinib, erlotinib and afatinib) and of ALK inhibitors (like crizotinib and ceritinib), respectively is associated with substantial improvements in progression-free survival (PFS), objective response rates (RRs) and possibly overall survival (OS) also.[5,6] Moreover, with such a molecularly targeted management approach, improvements in these 'physician-centred' outcomes (OS, PFS, RR) are achieved with lesser toxicity (as compared to standard chemotherapy regimens) and are associated with improvement in health-related quality of life (QOL) and symptom control which are important 'patient-centred' outcomes.[7,8] Another important change related to management of advanced/metastatic NSCLC that has occurred in the recent past has been the need to distinguish squamous and non-squamous histological subtypes in view of the differences in treatment approaches to these two subgroups.[9] Apart from the availability of specific molecularly targeted therapies for adenocarcinoma, pemetrexed, an anti-folate drug, has been proven to be the most effective and preferred third-generation agent for use in this histological subtype as first-line chemotherapy (in combination with a platinum agent) and subsequently as maintenance treatment (in the absence of disease progression with first-line chemotherapy).[10]

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For treatment naïve patients with stage IV NSCLC and good performance status (PS), histology guided platinum-based doublet chemotherapy for 4-6 cycles remains the standard of care when predictive molecular biomarkers for targeted therapy (namely sensitizing mutations in the EGFR gene for oral EGFR-TKIs and rearrangements in the ALK gene for crizotinib) have either not been assessed or are absent. Although radiation therapy plays an important role in management of medically inoperable stage I-II NSCLC and as part of concurrent chemoradiotherapy for locally advanced stage III NSCLC, its use (upfront or after initial systemic therapy) in stage IV NSCLC is limited to palliation of specific situations, like presence of superior vena caval (SVC) obstruction, symptomatic brain metastases or spinal cord compression, and severe pain that is uncontrolled or poorly controlled with analgesics prescribed as per the WHO stepladder algorithm for cancer pain management.[11] Even amongst radiation oncologists, considerable variations exist related to the timing and dosage schedule for use of radiation therapy in stage IV NSCLC as opposed to a near consensus on its usage in early and locally advanced disease.[12] The randomized trial by Sou and colleagues that appears in the current issue of the journal is an attempt to compare different dosage and fractionation schedules of thoracic external beam radiation therapy (EBRT) for palliation of pain in treatment naïve stage IV NSCLC. Randomization of 156 patients was done into three different schedules namely 17 Gy delivered in 2 fractions; 20 Gy delivered in 5 fractions and the standard 30 Gy delivered in 10 fractions. The first two schedules both led to completion of EBRT in one week while the third required two weeks. The authors reported similar magnitude of pain relief in all groups when assessed at three different time points (2, 6 and 12 weeks) after completion of thoracic EBRT. The three groups also had similar OS and improvements in QOL. Both OS and QOL are known to improve with chemotherapy and the lack of information in this study about percentage of patients who received subsequent chemotherapy (including regimens and number of cycles administered) remains a potential confounder.[13,14] We would have also expected the authors to have discussed the factors that led this population of newly diagnosed stage IV NSCLC patients to being treated upfront with radiation rather than with systemic therapy (chemotherapy/targeted therapy). The above-mentioned limitations notwithstanding, the important message from this study is that lesser fractions of thoracic EBRT (hypofractionation) are associated with similar results as are conventional radiation

schedules although it would have helpful if the profile of radiation therapy-associated toxicity (especially esophageal) observed in the three groups had been reported. Data from previously published studies and trials also indicate that in advanced NSCLC, protracted palliative thoracic EBRT offers no significant benefit for either symptom relief, improvement in QOL or OS when compared with short-term hypofractionated treatment schedules.[15-17] A systematic review that compared use of higher versus lower dose EBRT for symptom control in advanced lung cancer found similar results for control of individual symptoms (cough, chest pain, hemoptysis) although improvement in overall symptom burden was significantly better with higher dose EBRT.[18] One year (but not 2 years) OS rates have been observed to be better with higher dose EBRT.[18,19] In addition, the cost of therapy is significantly lower with shorter hypofractionation schedules.[20] The American Society for Radiation Oncology (ASTRO) in its evidence-based clinical practice guideline for use of palliative thoracic radiotherapy in lung cancer also states that lesser EBRT dose/fractionation schedules provide good symptomatic relief and may be used for patients requesting a shorter treatment course and/or in those with poor PS.[21] In resource-constrained settings as ours, wherein health care facilities tend to be overburdened including those wherein lung cancer patients are treated, use of hypofractionated schedule offers several potential advantages.[22,23] First, it reduces the number of hospital visits that patients are required to undertake while undergoing radiation therapy. Second, it reduces the number of sessions that treating radiation oncologists need to schedule for a given patient. Third, it reduces the overall length (duration) of radiation therapy (faster completion of treatment from time of initiation). Fourth, it also reduces the direct costs related to radiation therapy and possibly even the indirect costs by reducing radiation therapy-related toxicity.

It is important to realize that palliative interventions are not merely those which target the disease *per se* (e.g. chemotherapy or radiation therapy) but are also those in which symptom-based management is undertaken e.g. use of medical thoracoscopy for malignant pleural effusions and use of interventional pulmonology procedures for airway obstruction.[24,25] Since the publication of the randomized trial by Temel and colleagues involving metastatic NSCLC patients, there has been renewed interest and enthusiasm in the concept of early integration of palliative care with standard oncological care.[26] Traditional versus early palliative care models differ from each other substantially in the sense that the former approach is focused on institution of palliative care only after life-prolonging or curative treatment is no longer being administered while in the latter approach (integrated model), both palliative care and life-prolonging care are provided throughout the course of disease.[27] This is important because palliative care is frequently misinterpreted as being synonymous with end-of-life care while in true terms, it aims to relieve suffering, in all of its dimensions, throughout the course of a patient's illness. In the trial by Temel *et al*., the intervention arm (early integrated palliative care with standard oncological treatment) showed significant improvement in symptoms, QOL (spiritual and end-of-life domains) and even OS as compared to the conventional arm (standard oncological treatment only).[26] These gains were achieved with a simultaneous reduction in the utilization of health care services and in the overall cost of cancer care. Some of these improvements in patient outcomes have been replicated subsequently in a larger trial as well.[28] These results have led to generation of a consensus opinion that all metastatic NSCLC patients should be offered concurrent palliative care and standard oncological care at initial diagnosis in view of its immense potential for improving 'patient-centred' outcomes and reducing burden on caregivers (typically immediate family members).[29]

There have been suggestions that for Asia, wherein countries can range from being resource-poor (resource constrained) to resource-rich, the concept of integrating palliative care with standard oncological care could range from *basic* to *maximal* depending upon the level of resources available.[30] Even at the *basic* level, pain should be routinely assessed - '*fifth vital sign*' - and managed with appropriate analgesic prescriptions. In a comprehensive approach, the key interventions in palliative care (integrated with standard oncological treatment) actually encompass five major domains: (1) Illness understanding, (2) Symptom management, (3) Treatment decision making, (4) Illness coping (patient and family caregiver), and (5) Care planning (referrals and drug prescriptions).[31]

The American Society of Clinical Oncology (ASCO; www.asco.org) and the European Society for Medical Oncology (ESMO; www.esmo.org) which are two of the most renowned professional oncology bodies in the world offer opportunities to physicians and oncologists in developing countries to enhance their knowledge about palliative care. The Conquer Cancer Foundation of the ASCO offers the International Development and Education Award (IDEA) (http://www.conquercancerfoundation.org/cancer-professionals/grants-awards/international-development-and-education-awards) and its associated IDEA-Palliative Care. The ESMO offers the Palliative Care Fellowship (http://www.esmo.org/Career-Development/Oncology-Fellowships/Fellowship-Offers/Palliative-Care). Our personal experience with both of the above has been very encouraging in terms of the insight into evidence based clinical approach and potential for improvement in cancer management that such experiences provide. Despite being highly competitive globally, we recommend that individuals who have a keen interest in oncological palliative care should consider applying for these annual awards/fellowships.

Navneet Singh, Digambar Behera

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh (U.T.), India

E-mail: navneetchd@hotmail.com

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