Clinical Trials Need to Control for the Influence of Palliative Care on Outcomes

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To insure standardization of all aspects of care during the conduct of a clinical trial, clinical trials should include guideline-based criteria for the management of all symptoms of cancer and its treatment, and failure to adhere to any of the standards for symptom management during the conduct of the trial should result in an equal level of protocol violation.

The article by Kavitha Ramchandran and Jamie Von Roenn on page 13 of this issue of ONCOLOGY expertly relates how the quality of life of patients and caregivers—and overall survival—are improved when the symptoms of cancer and its treatment are controlled. Improved survival and clinical benefit are key endpoints for clinical trials. Given its impact on survival, specifying parameters for symptom management should be considered as important as controlling for other clinical factors, such as cytopenias, during clinical trials.

The influence of symptom control on the rate of survival in Temel's landmark study in newly diagnosed stage IV lung cancer patients has especially important implications for early-phase clinical trials. In this study, all patients received usual oncologic care, but half of the patients also received concurrent palliative care. Patients in the palliative care arm, who received less aggressive oncologic care at the end of life, had a statistically significant improvement in overall survival (8.9 months vs 11.6 months, \(P = .02\)).

Another prospective randomized controlled palliative care study—conducted earlier by Smith in advanced-stage cancer patients—showed, as an unexpected finding, a similar improvement in overall survival. This study compared the quality of pain management with an implanted intrathecal (IT) drug delivery system vs medical management (MM). IT administration of analgesics achieved a 20% or greater reduction in pain and analgesic-related toxicities in 57.7% of patients vs 37.5% in those who received MM (\(P = .02\)). The mean pain score was reduced by 52% with IT vs only 17% with MM (\(P = .055\)). Surprisingly, 53.9% of the IT group were alive at 6 months, compared with 37.2% of the MM group (\(P = .06\)).

These studies demonstrate the potential influence of symptom management on survival outcomes in clinical trials. In light of these findings, the following should be considered. First, symptoms should be included in the multivariate analysis of clinical outcomes during a clinical trial. Performance status, an accepted prognostic factor reflecting symptoms that affect function, is routinely specified in study inclusion criteria. However, patient-reported symptoms or performance status are rarely correlated with survival outcomes during or after the trial. A subset analysis based on symptoms and/or performance status during or after the trial could provide valuable insight into the therapy's mechanism of action.

Second, using the control of emesis as a precedent, the management of other symptoms during clinical trials should be specified within the protocol. Improved clinical tolerance, through the
standardization of supportive care, reduces toxicities and interruptions in therapy that can adversely affect every outcome, including survival. Furthermore, inter-institutional variability of symptom control can skew toxicity rates, and potentially overall survival rates, based on the number of patients that an institution enters in a clinical trial.

Third, and most important, is the limited amount of effort that needs to be invested to improve symptom control and survival. The palliative care intervention in the Temel study involved only one hour a month yet achieved a statistically significant improvement in overall survival. Tolerance of therapy was significantly improved during a course of head and neck radiation therapy with a brief daily nursing check that promptly addressed symptoms as they developed.[3] With the nursing check and only a 3% difference in opioid use between the groups, patients reported a 35% decrease in pain noted most or all of the day (58% vs 23%), and a mean weight loss of more than 5 kg was recorded in only 16% of the nursing intervention group vs 57% of patients receiving standard care.[3]

Nationally accredited guidelines exist for all symptoms of cancer and its treatment; these guidelines are intended for use by practicing oncologists, requiring only limited involvement by palliative care specialists. Selective symptom management that expertly prevents emesis and cytopenias while inadequately managing other symptoms, such as pain, is not acceptable oncologic practice.

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References:

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