ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

β-Blockers in Non–Small Cell Lung Cancer

Daniel Gomez, MD
Assistant Professor
Department of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

H&O Which treatments are used in non–small cell lung cancer, and how effective are they?

DG Multiple treatments are used in non–small cell lung cancer. It is one of the diseases for which we use trimodality treatment, so surgery, radiation, and chemotherapy all play a role depending on the stage.

In our study from The University of Texas MD Anderson Cancer Center, published in the *Annals of Oncology* earlier this year, we looked at locally advanced patients. That is, our study focused on patients who were not surgical candidates and who were treated with radiation alone or radiation plus chemotherapy. In this scenario, most studies have shown that 5-year survival rates range from approximately 10–25%.

H&O What is the molecular mechanism on which clinical studies involving β-blockers are based? Is there any evidence pertaining to how β-blockers are thought to affect angiogenesis, cancer cells, and the tumor microenvironment?

DG Several preclinical studies—performed in either cells or mouse models—have looked at the adrenergic pathway of β-blockers and its effect on cancer. In addition, a number of preclinical studies have shown that β-blockers can reverse the proliferation of lung cancer cells by affecting both β-adrenergic and nicotinic receptors. They can also reduce cancer progression and the invasion of cancer cells by affecting the expression of cytokines, which are substances released in the body that can affect the ability of cancer cells to invade. It is because of studies outlining these mechanisms that there has been an increase in clinical analyses assessing the effect of β-blockers in patients with various types of cancer.

H&O How common is the use of β-blockers in patients with non–small cell lung cancer?

DG β-Blockers still are not used for the actual treatment of lung cancer, although a significant portion of patients require β-blockers for another comorbidity, such as hypertension or heart disease, where β-blockers do play a role. Approximately 20% of the patients in our study used β-blockers—again, not for lung cancer, but for other conditions for which they are indicated. For this reason, our study examines "incidental" β-blocker use, meaning that the medication was not given in the context of any trial.

H&O What have previous studies shown regarding the use of β-blockers in patients with cancer?

DG Results from several studies have suggested that β-blockers can be used to reduce the rate of disease recurrence in other malignancies, primarily breast cancer and malignant melanoma. In our study, we cited several analyses that looked at the relationship between β-blockers and cancer. These analyses also examined the outcome of patients who took β-blockers for reasons unrelated to cancer, and were retrospective, single-institution studies or population-based studies using data that are publicly available. In one of the largest studies (by Barron and colleagues in the *Journal of Clinical Oncology*), which examined data on patients with breast cancer in a national registry, 595 patients taking a β-blocker were compared with 4,738 patients who were not taking a β-blocker. The researchers found that patients taking a β-blocker were less likely to present with advanced disease and less likely to die of breast cancer. The authors concluded that β-blocker use was associated with reduced

rates of advanced disease and breast cancer mortality. Studies like these prompted our analysis of looking at the effect of β-blockers in lung cancer, which had not previously been examined in such a large patient cohort.

H&O Could you please describe the design of your recent study?

DG Our study included 722 patients with non–small cell lung cancer who received definitive radiation with or without chemotherapy. Most patients did receive chemotherapy. The primary purpose of this study was to assess whether the use of β-blockers was associated with distant metastasis and subsequent survival outcomes for patients with non–small cell lung cancer who were treated with definitive radiation. We controlled for factors that included extent of disease, performance score, histologic type, and use of other medications. Study endpoints included locoregional progression-free survival, distant metastasis-free survival, disease-free survival, and overall survival.

We found that the use of β-blockers did not affect locoregional progression-free survival, but was associated with improved rates of distant metastasis-free survival, disease-free survival, and overall survival. Such correlations held up even after adjusting for the aforementioned factors. These findings are concordant with those of previous preclinical studies, and suggest that β-blockers have specific effects on the metastatic cascade.

H&O Were there any differences between selective and nonselective β-blockers?

DG Although the choice of β-blockers may be important, we had an insufficient number of patients in each arm who took selective versus nonselective β-blockers to truly elucidate any difference. That is something we cannot address right now.

H&O How do these findings compare with those of previous studies?

DG While several prior studies had suggested that β-blockers could improve outcomes for patients with cancer, the results were somewhat mixed. For instance, the study by Barron and colleagues demonstrated a correlation between β-blocker use and improved survival. In contrast, in a study from the United Kingdom by Shah and coworkers that identified patients with hypertension and a new diagnosis of cancer in a primary care database, the researchers compared 1,406 patients who were receiving β-blockers regularly with 2,056 patients who were receiving a different antihypertensive medication. They did not observe improved survival among the patients in the β-blocker group.

Some of this variation may be due to the fact that there were differences in the type of β-blockers used, as well as the fact that different cancers were being treated. Factors such as these are difficult to control in retrospective studies, in which the data are not being collected as patients are treated.

H&O What were the limitations and strengths of your study?

DG As alluded to above, the primary limitations of this study were that it was retrospective and single-institution; we relied on patient medical records rather than documenting β-blocker use during treatment. However, the study was very large and it contained a relatively homogeneous population. Patients had similar types and stages of cancer, and all were treated in a similar fashion with regard to radiation doses, prescription constraints, and definitive radiotherapy at a single institution. I believe that our results warrant and emphasize the need for prospective studies to investigate these findings further.

H&O Do your study results have implications for clinical care?

DG I do not think that there are immediate implications for clinical care because of the limitations of the study, being single-institution and retrospective. Ultimately, there could be implications for clinical care, if such findings carry over into prospective analyses, as well as analyses at other institutions.

The primary take-home point is that this large, retrospective, single-institution study showed that β-blockers have a clinical benefit, and this finding is supported by preclinical data and by other retrospective studies. Taken together, this can be seen as a call to develop prospective, larger studies with other institutions to look at this relationship. If these findings are validated, future studies could examine the optimal duration and timing of β-blocker use.

Suggested Readings

Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population-based study. *J Clin Oncol*. 2011;29:2635-2644.

Lemeshow S, Sørensen HT, Phillips G, et al. Beta-blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. *Cancer Epidemiol Biomarkers Prev*. 2011;20:2273-2279.

Shah SM, Carey IM, Owen CG, et al. Does beta-adrenoceptor blocker therapy improve cancer survival? Findings from a population-based retrospective cohort study. *Br J Clin Pharmacol*. 2011;72:157-161.

Wang HM, Liao ZX, Komaki R, et al. Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. *Ann Oncol*. 2013;24:1312-1319.