Statin Use and Survival in Resectable Pancreatic Cancer: Confounders and Mechanisms

Livia Archibugi, MD[1], Gabriele Capurso, MD, PhD[1] and Gianfranco Delle Fave, MD[1]

doi:10.1038/ajg.2015.412

To the Editor: We read with great interest the paper by Wu *et al.* (1) demonstrating that, among patients with surgically treated pancreatic cancer, statin users, especially those employing moderate-to-high dosages of simvastatin, had a significantly improved overall survival, also when this was adjusted for multiple confounders. This is an interesting finding, confirmed by similar recent results from the SEER-Medicare database (2). Although we agree that the use of statins in patients operated for pancreatic cancer merits further investigation, we think that some additional points might need discussion to help clarifying the authors' findings.

A first point regards the possible activity of drugs other than statins, such as aspirin or metformin, against pancreatic cancer. As many patients use a combination of these drugs, one might speculate that the association between simvastatin and overall survival in resected pancreatic cancer patients might also be explained by the concomitant use of aspirin or metformin, or that these drugs might result synergistic, as hypothesized for colorectal cancer (3). We wonder whether the authors had access to data on aspirin or metformin use for their population.

A second point regards the very high 45% rate of simvastatin or lovastatin users reported by the authors. This figure is different from that of many European countries, thus possibly limiting the attributable fraction of cases for whom the observed findings can be replicated.

We interrogated our single-center database of 356 consecutive pancreatic cancer patients to analyze these two issues and found no protective effect of the use of either statins, aspirin, metformin, or any of their combination in terms of overall survival. As expected, however, only 17.7% of our patients used statins (5.6% simvastatin). Notably, when considering only 85 resected patients, still no difference was found between active users and non-users of statins (hazard ratio (HR) 1.06; 95% confidence interval (CI) 0.5–2.2) or aspirin (HR 0.9; 95% CI 0.4–1.9), metformin (HR 0.45; 95% CI 0.04–4.2), or statin and aspirin combination (HR 0.54; 95% CI 0.2–1.4).

Finally, as far as the mechanisms by which simvastatin might improve survival, the authors do not cite the possible direct effect on the risk of venous thromboembolism. Venous thromboembolism is a rather frequent event in patients with pancreatic cancer, with serious consequences also in terms of survival, and the use of both statins and aspirin seems to reduce this risk in cancer patients (4).

CONFLICT OF INTEREST

Specific author contributions: Livia Archibugi collected data of patients and wrote the manuscript; Gabriele Capurso contributed with analysis and interpretation of data, and revision of the manuscript; Gianfranco Delle Fave performed critical revision of the manuscript for important intellectual content.
Financial support: None.
Potential competing interests: None.

REFERENCES

1. Wu BU, Chang J, Jeon CY *et al.* Impact of statin use on survival in patients undergoing resection for early-stage pancreatic cancer. Am J Gastroenterol 2015;110:1233–9.
2. Jeon CY, Pandol SJ, Wu B *et al.* The association of statin use after cancer diagnosis with survival in pancreatic cancer patients: a SEER-Medicare analysis. PLoS One 2015;10:e0121783.
3. Zanders MM, van Herk-Sukel MP, Vissers PA *et al.* Are metformin, statin and aspirin use still associated with overall mortality among colorectal cancer patients with diabetes if adjusted for one another? Br J Cancer 2015;113:403–10.
4. Lötsch F, Königsbrügge O, Posch F *et al.* Statins are associated with low risk of venous thromboembolism in patients with cancer: a prospective and observational cohort study. Thromb Res 2014;134:1008–13.

[1]Department of Medicine and Psychology, Digestive and Liver Disease Unit, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy. Correspondence: Gianfranco Delle Fave, MD, Department of Medicine and Psychology, Digestive and Liver Disease Unit, Sant'Andrea Hospital, Sapienza University of Rome, Via di Grottarossa, 1035, 00189 Rome, Italy. E-mail: gianfranco.dellefave@uniroma1.it

De novo Malignancy and Recurrent Alcoholic Cirrhosis Account for 70% of Deaths in Patients Transplanted for End-Stage Alcoholic Liver Disease

Jef Verbeek, MD, PhD[1,2], David Cassiman, MD, PhD[1] and Frederik Nevens, MD, PhD[1]

doi:10.1038/ajg.2016.10

To the Editor: We read the article by Dumortier *et al.* (1) with interest. This elegant study, in a large number of patients with a long-term follow-up, raises the concern regarding recurrent alcoholic cirrhosis (RAC) after liver transplantation (LTx) for end-stage alcoholic liver disease (ALD).

In our single center study, 204 patients were transplanted for ALD between 1994 and 2011, of which 193 patients survived >6 months after LTx (2). Mean follow-up after LTx was 5 years. A total of 27.5% (53/193) of the patients had an alcoholic relapse defined as any alcohol use. In support of the findings by Dumortier *et al.* (1), 7.5% (4/53) of them developed biopsy proven RAC, despite our significantly shorter follow-up after LTx.

However, as briefly touched by the authors, *de novo* malignancy and not RAC is the major determinant of mortality in patients transplanted for ALD. In our