C-Reactive Protein and Chronic Inflammation
— Is It a Novel Therapeutic Target for Subsequent Cancer Death in Patients With Coronary Artery Disease? —

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High-sensitivity C-reactive protein (hs-CRP) is an established marker of inflammation, and increased hs-CRP is related to subsequent cardiovascular events. Wada et al analyzed a large registry of Japanese patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), and found that higher preprocedural levels of hs-CRP increased all-cause mortality and the incidence of major adverse cardiac events including all-cause death, acute coronary syndrome, and target vessel revascularization, suggesting the significance of preprocedural hs-CRP measurement and the role of chronic inflammation for long-term risk assessment in Japanese patients with CAD treated by PCI.

Chronic inflammation plays an important role in the development of not only atherosclerotic disease, including CAD, but also cancer, including tumor invasion, progression, and metastasis. For example, a persistent inflammatory response is pathologically closely associated with the chronic bronchitis induced by cigarette smoking, asbestos, silica etc., resulting in lung cancer. Higher serum CRP levels are reported to increase the incidence and mortality of any type of cancer as well. Allin et al reported that elevated levels of CRP were associated with increased risk of cancer of any type, of lung cancer, and possibly of colorectal cancer in a Danish general population without cancer diagnosis at baseline. Therefore, chronic inflammation as evaluated by serum CRP level is important in risk stratification for both CAD and cancer. However, the predictive value of hs-CRP for future cancer risk in patients with CAD remains unknown.

In this issue of the Journal, Endo et al seek to clarify the significance of hs-CRP on long-term mortality from malignancy in patients with stable CAD undergoing PCI. They used a single-center prospective registry to examine a total of 2,867 consecutive patients (mean age, 67 years, 83% male) with stable CAD treated by PCI from 2000 to 2016. The median value of hs-CRP before index PCI was 0.10 mg/dL. During the median follow-up period of 5.8 years, 416 deaths occurred (15%), including 149 cardiovascular deaths (5%) and 115 cancer deaths (4%). Among the cancer deaths, gastrointestinal cancer (n=60) and lung cancer (n=24) were common. Smokers had higher baseline hs-CRP levels and a higher incidence of cancer death than non-smokers. Kaplan-Meier curves clearly show that patients with higher baseline hs-CRP levels had higher all-cause mortality and cancer mortality. This trend is also seen for both gastrointestinal and lung cancer deaths.

Furthermore, multivariable Cox regression analysis shows that higher hs-CRP levels (hazard ratio [HR] 1.7, P<0.001), as well as older age (HR 1.1, P<0.001), history of cigarette smoking (HR 2.4, P<0.001), and aspirin use (HR 0.46, P=0.044) were independently associated with cancer mortality.

This study is very important. As shown by the results, the number of cancer deaths was almost similar to that of cardiovascular deaths among patients with stable CAD treated by PCI. Preceding studies have already confirmed the predictive value of hs-CRP for subsequent cardiovascular events. As far as we know, this is the first study to demonstrate a clear relationship between baseline hs-CRP and future cancer death, particularly in Asian patients.

Further study is required for future perspectives. We need to clarify which type of cancer can be predicted by measurement of hs-CRP. In this study, the majority of cancers were gastrointestinal cancer and lung cancer. However, this result is in line with epidemiological data for the Japanese general population, and therefore it is unclear whether baseline hs-CRP is specifically associated with gastrointestinal and lung cancers. For example, cigarette smoking induces chronic inflammation and is a strong risk factor for both CAD and cancer (particularly, lung cancer). So, it is possible that an increased hs-CRP level is simply a result of cigarette smoking, and does not directly reflect cancer occurrence. It is not easy to conclude the causal relationship between chronic inflammation and cancer development. The next topic is how to manage patients with higher baseline hs-CRP levels and whether anti-inflammatory therapy can prevent cancer deaths after PCI. Aspirin (acetylsalicylic acid) and statins (HMG-CoA reductase inhibitors) are widely used in patients with CAD, and both known to have anti-inflammatory effects. Several
studies show the potential of these medications in reducing cancer incidence. In the results of the study of Endo et al., aspirin use was significantly associated with and statin use tended to be associated with a lower risk of subsequent cancer death in patients with CAD undergoing PCI. Attention should be paid to these results. Furthermore, the CANTOS trial sheds light on this point. It showed that anti-inflammatory therapy targeting interleukin-1β by using the interleukin-1β inhibitor (canakinumab) was shown to reduce not only the incidence of recurrent cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death), but also deaths from lung cancer, in patients with a prior history of myocardial infarction. The underlying mechanisms for the association between use of interleukin-1β inhibitor and reduced risk of lung cancer still remain unclear, and further study is required to confirm the effect of prevention of cancer by using anti-inflammatory treatment.

Today, oncocardiology attracts clinical interest. Most topics in this field focus on cardiovascular events in patients with malignancy, such as cardiotoxicity of anti-neoplastic medications, thrombotic events in patients with malignancy etc. On the other hand, as the present study has clarified the subjects at high-risk for cancer death among patients with stable CAD undergoing PCI. This study is important and informative for the further management of cardiovascular disease.

References