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Original Research

The difference in association between aspirin use and other thrombocyte aggregation inhibitors and survival in patients with colorectal cancer

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Abstract ***Background:*** Several studies have suggested that the association between aspirin and improved cancer survival is mediated through the mechanism of aspirin as thrombocyte aggregation inhibitors (TAI). The aim of this study was to provide epidemiological evidence for this mechanism assessing the association between overall survival and the use of aspirin and non-aspirin TAI in patients with colorectal cancer.
Methods: In this observational study, data from the Netherlands Comprehensive Cancer Organisation were linked to PHARMO Database Network. Patients using aspirin or aspirin in combination with non-aspirin TAI (dual users) were selected and compared with non-users. The association between overall survival and the use of (non-)aspirin TAI was analysed using Cox regression models with the use of (non-)aspirin TAI as a time-varying covariate.
Results: In total, 9196 patients were identified with colorectal cancer and 1766 patients used TAI after diagnosis. Non-aspirin TAI were mostly clopidogrel and dipyridamole. Aspirin use was associated with a significant increased overall survival and hazard ratio (HR) 0.41 (95% confidence interval [CI] 0.37–0.47), and the use of non-aspirin TAI was not associated with survival of HR 0.92 (95% CI 0.70–1.22). Dual users did not have an improved overall survival when compared with patients using solely aspirin.
Conclusions: Aspirin use after diagnosis of colorectal cancer was associated with significantly lower mortality rates and this effect remained significant after adjusting for potential

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confounders. No additional survival benefit was observed in patients using both aspirin and another TAI.

1. Introduction

1.1. Evidence before this study

There is growing evidence that aspirin use after diagnosis could reduce metastatic spread and increase the survival of patients with colorectal cancer. A recent systematic review and meta-analyses of Elwood *et al.* showed a reduction of approximately 25% in colorectal cancer–specific mortality (HR 0.71, confidence interval [CI] 0.58–0.87) and 20% in all-cause mortality (HR 0.80, CI 0.70–0.92) [1]. The mechanism of action of aspirin in colorectal cancer–specific mortality was previously thought to be a result of the prevention of colonic adenomas and, subsequently, less cancer development from these adenomas. However, meta-analyses of large secondary cardiovascular prevention trials show a larger effect on colorectal cancer–specific mortality than would be expected if only adenomas were prevented [2].

Randomised controlled trials are eagerly awaited to provide a decisive answer on the effect of aspirin as adjuvant therapy for cancer: ASCOLT trial (NCT00565708), Add-Aspirin trial (ISRCTN74358648) and Aspirin trial (NCT02301286).

1.2. Biological mechanism of aspirin

The current described mechanisms of action of aspirin on cancer are inhibition of tumour growth and angiogenesis, delay of metastatic spread, abrogation of invasiveness, improvement of cellular apoptosis and enhancements of DNA mismatch repair [1]. Previous studies attempted to unravel the mechanism of action of aspirin with the identification of a specific biomarker, which could concurrently be used to predict the effectiveness of aspirin as adjuvant therapy. PIK3CA mutation status, HLA class I antigen expression and COX-2 overexpression have been suggested to play a role in this mechanism; however, study results are heterogeneous [3].

1.3. Thrombocytes and cancer

Thrombocytes become activated and aggregated by cancer cells via various mediators, such as direct cell-cell contact, coagulant disturbances and soluble mediators (thromboxane A_2) [4]. Thrombocyte membranes consist of adhesion molecules promoting adhesion; for example, to other thrombocytes and the vascular wall. Thrombocyte activation induced by cancer cells promotes several steps in cancer progression, such as cancer metastasis, tumour proliferation and angiogenesis. In this manner, cancer cell–bound thrombocytes form a cloak around the cancer cells and protect the cancer cells from immune surveillance, including cytolysis by natural killer cells [4]. Although the pathogenesis is not clear, thrombocytosis in colorectal cancer patients has been observed to be associated with a poor cancer prognosis [5]. This could suggest that inhibiting the aggregation of thrombocytes could be a new therapeutic target for cancer therapy.

The effect of aspirin on cancer mortality has also been suggested to be mediated through the ability of aspirin to inhibit thrombocyte aggregation [4,6,7]. The aim of this study was to provide epidemiological evidence for the hypothesised thrombocyte-mediated mechanism of aspirin through studying other thrombocyte aggregation inhibitors (TAI).

2. Patients and methods

2.1. Study population

Data were obtained from the Netherlands Comprehensive Cancer Organisation (IKNL) and linked on a patient level to the PHARMO Database Network, covering a demographic region in the South-eastern part of the Netherlands of approximately 1.5 million inhabitants (formerly known as the Eindhoven Cancer Registry, ECR). Connecting drug dispensing records from the PHARMO Database Network to individual cancer survival data from IKNL, allows drug use to be analysed per (cancer) patient. The PHARMO Database Network is population-based and combines data from healthcare settings in the Netherlands. For this study, data from the outpatient pharmacy database was used. The construct and validity of the IKNL-PHARMO cohort have been described elsewhere [8]. Patients with colorectal cancer older than 18 years and diagnosed between January 1998 and December 2011 were included. Patients were informed about the registration and registered, unless they objected to be registered, and therefore informed consent for this study was not applicable. The vital status (dead/alive) of patients was obtained by the municipal population registry and was linked to IKNL. Follow-up of this study was until 31st December 2012.