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Letter to the Editor

In response to Ham et al.: Antibiotics effect on outcome in head and neck cancer

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Platinum-based chemoradiotherapy (CRT) is the standard of care for locally advanced head and neck cancer (LAHNC) with overall survival (OS) of about 40% at 5 years but with high incidence of acute and late toxicity such as mucositis, fibrosis, dysphagia and aspiration pneumonia.

Ham JC et al. [1] in a phase II randomised study on 95 patients showed that 5 weeks of prophylactic amoxicillin/clavulanic acid (from day 29 after the start of treatment until 14 days after completion of chemoradiotherapy) can reduce hospitalisations (39.6% versus 19.1% in the standard group versus the prophylaxis group, respectively, $p = 0.03$), although it cannot prevent pneumonia (45.8% vs 46.8% in the standard group versus the prophylaxis group, $p = 0.54$).

It might be argued that in the prophylaxis group, only 61.7% completed the amoxicillin/clavulanic acid prophylaxis as planned, predominantly because of poor compliance, which is partly due to this specific patient population.

The authors also showed a significant difference in costs was found, with an average reduction of €1425 per patient in favour of the prophylaxis group.

They concluded that prophylactic antibiotics during CRT tend to be cost-effective because although it did not reduce the incidence of pneumonias, it did reduce hospitalisation rates and episodes with fever significantly (Ham et al [1]).

Cancers, which for a long time were thought to be essentially sterile, evolve in close association with bacterial species. The human gut microbiome modulates many host processes, including metabolism, inflammation and immune and cellular responses. It is becoming increasingly apparent that the microbiome can also influence cancer outcomes (Zitvogel et al [2]).

LAHNC patients (LAHNCPs) have several risk factors for deregulated microbiome including smoking and alcohol consumption, diet and poor oral hygiene. Almost all LAHNSCPs receive systemic antibiotic therapy during CRT for fever, central vein catheter infection, mucositis, etc.

Mirabile et al. [3] in a retrospective analysis on 352 health care–associated infections among LAHNCPs reported that male sex, age <65 years, important comorbidities, smoking, proton pump inhibitors (PPIs), prophylaxis, central venous catheter (CVC), more locally advanced disease and at least 3 weeks of treatment with CRT were risk factors. Moreover, analysing infection rates over 2 periods (January 2005 to December 2009 and January 2010 to November 2012), the authors described an increase over time, with corresponding increases in gram-negative pathogens and resistant strains (Mirabile et al [3]).

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Antibiotics negatively impact cancer prognosis; the first association was reported in a Finnish study on an extensive cohort that stated an increased risk of cancer (Kilkkinen et al [4]).

However, bacteria resistance is a challenge as well as the impact of an antibiotic-altered microbiome on outcomes. In this complicated population (LAHNCPs), the suggestion is to not overexpose to antibiotics to reduce bacteria resistance and ensure no interaction on therapies' efficacy.

Moreover, in the era of immunotherapy, this issue will be more and more important; as several studies confirmed that microbiome has a key role both on treatment response and prognosis (Viaud et al [5]).

We observed in unpublished series on 235 chemoradiotreated LAHNCPs that those who received longer than 20 days of antibiotics had a negative trend for outcomes (OS: 23.4 vs 39.2 months; $p = 0.07$).

In preclinical models, the host response to cancer treatment has been improved by modulating the gut microbiome. On the one hand, antibiotics may reduce cancer outcomes; on the other hand, antimicrobial agents or their products have the potential to shrink tumours. Actually, the microbiome could also negatively influence cancer prognosis and metastasization through pro-oncogenic bacteria (Derosa et al [6]).

In conclusion, we found the article of Ham et al. [1] to be very interesting, but an analysis of oncological outcome is mandatory because antibiotic therapy may impact cancer outcomes both positively and negatively. Moreover, modulation of antibiotic-related dysbiosis and gut microbiome need additional study.

Conflict of interest statement

None declared.

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