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Update of Systematic Reviews and Meta-Analyses Studying the Association Between Antibiotic Use and Clinical Outcomes of Cancer Patients Treated with Immune Checkpoint Inhibitors

Gérard Zalcman[1,2], Athéna Crespin[3], Julie Cervesi[3], Clément Le Bescop[3], Renaud Buffet[3], Jean de Gunzburg[3], Pierre-Alain Bandinelli[3]

(1) Department of Thoracic Oncology and CIC1425, Hôpital Bichat-Claude Bernard, Assistance Publique Hôpitaux de Paris, Université de Paris, Paris, France,

(2) U830 INSERM "Genetics and Biology of Cancers, ART Group", Curie Institute, Paris, France, (3) Da Volterra, Paris, France

BACKGROUND

- Experimental studies involving mouse tumor models and fecal microbiota transplant from cancer patients have suggested that intestinal dysbiosis impacts the response to anti-PD(L1) mAb[1,2,3].
- Prior clinical research has strongly suggested that systemic antibiotic (ABX) exposure impacts the intestinal microbiota and may result in suboptimal immune checkpoint inhibitor (ICI) treatment outcomes.
- In 2020, our team published a systematic review and meta-analysis[4] showing that ABX use was associated with a decrease of the survival of patients diagnosed with non-small-cell lung cancer (NSCLC) and treated with ICI.
- Since then, a number of publications including patients with other cancer types were published. We decided to conduct a new systematic review and meta-analysis on the impact of ABX on the efficacy of ICI in all types of cancer.

METHODS

- Medline (through PubMed), the Cochrane Library and major oncology conferences proceedings were systematically searched to identify abstracts, posters, articles, systematic reviews and meta-analyses studying the impact of ABX use on the clinical outcomes of cancer patients treated with ICI.
- Studies were deemed eligible for inclusion when they mentioned a hazard ratio (HR) or Kaplan–Meier curves for overall survival (OS) or for progression-free survival (PFS) based on antibiotic exposure.
- Pooled HR for OS and PFS were calculated according to cancer types and according to time windows of ABX exposure

RESULTS

65 studies reported data for OS (23,146 patients) and 45 for PFS (14,689 patients). The overall pooled HR was 1.65 (95% confidence interval [CI]: 1.46-1.87) for OS and 1.44 (95% CI: 1.27-1.64) for PFS, confirming a significantly reduced survival in cancer patients treated with ICI and exposed to ABX. The detailed analysis in subgroups according to cancer type (Figure 1) demonstrates a decreased survival for most cancers.

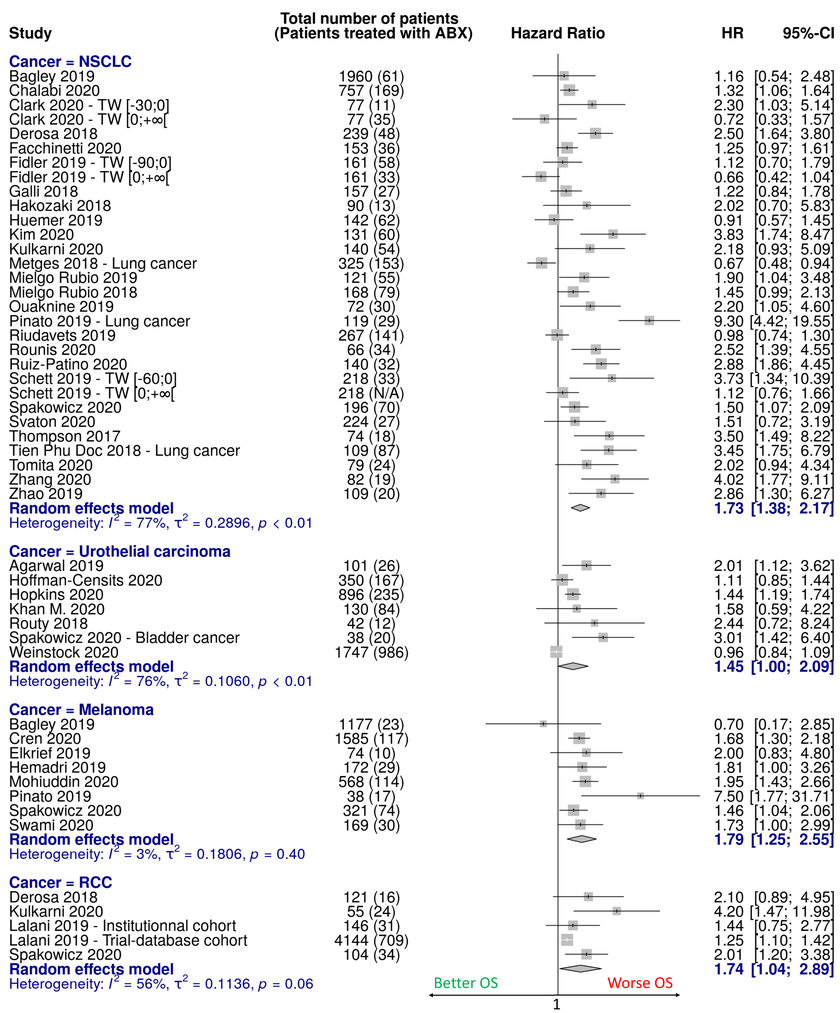

Figure 1: Forest plots of hazard ratios for OS of cancer patients exposed or not to antibiotics, according to cancer type

ABX, Antibiotic; HR, Hazard Ratio; CI, Confidence Interval; TW Time Window; RCC, Renal Cell Carcinoma

The detailed analysis in subgroups according to time windows of ABX exposure (Table 1) suggests that the deleterious effect of ABX is stronger when the exposure happens shortly before and after the start of the ICI treatment.

Time Window of Exposure to ABX in Relation to ICI Treatment Initiation (Days)	HR OS [95% CI] N studies (N patients)	HR PFS [95% CI] N studies (N patients)
-∞ -90 -60 -30 **0** 30 60 90 120 +∞	1.35 [0.85-2.14] 4 (1,141)	1.03 [0.99-1.07] 2 (511)
-∞ -90 -60 -30 **0** 30 60 90 120 +∞	1.85 [1.26-2.73] 7 (975)	1.74 [0.93-3.24] 6 (880)
-∞ -90 -60 -30 **0** 30 60 90 120 +∞	2.32 [1.61-3.34] 12 (2,326)	1.55 [1.19-2.02] 10 (2,123)
-∞ -90 -60 -30 **0** 30 60 90 120 +∞	2.12 [0.80-5.65] 3 (278)	1.81 [1.30-2.51] 6 (460)
-∞ -90 -60 -30 **0** 30 60 90 120 +∞	1.63 [1.43-1.86] 27 (15,798)	1.52 [1.23-1.86] 17 (9,867)
-∞ -90 -60 -30 **0** 30 60 90 120 +∞	1.81 [1.23-2.68] 7 (1,800)	1.67 [0.93-3.01] 4 (552)
-∞ -90 -60 -30 **0** 30 60 90 120 +∞	1.47 [0.89-2.44] 11 (1,616)	1.13 [0.66-1.91] 6 (1,123)

Statistically significant. Non statistically significant.

Table 1: Hazard ratios for OS and PFS of cancer patients exposed to ABX versus not exposed to ABX, according to the ABX exposure time window

CONCLUSION & PERSPECTIVES

The meta-analysis confirms the previously reported deleterious effect of ABX on outcomes of ICI-treated cancer patients.

The impact of ABX exposure seems stronger for melanoma and NSCLC and when the exposure to ABX happens shortly before and after the initiation of the ICI treatment. Later ABX use during ICI treatment course does not seem to alter survival or to a lesser extent. The topic deserves further research to uncover if the effect will stand with 1st line use of ICI together with chemotherapies, elucidate the mechanisms at stake and improve the care of patients.

CONFLICTS OF INTEREST

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CONTACTS

Da Volterra (Paris, France)
athena.crespin@davolterra.com

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