Evolution of plasma vitamin $B_{12}$ in patients with solid cancers during curative versus supportive care

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Submitted: 30 June 2021; Accepted: 6 August 2021
Online publication: 3 September 2021

Arch Med Sci 2021; 17 (6): 1811–1815
DOI: https://doi.org/10.5114/aoms/140974
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Abstract

Introduction: The direction of the causal link between solid cancers and elevated plasma vitamin $B_{12}$ ($B_{12}$) remains uncertain.

Methods: We retrospectively included patients having two $B_{12}$ measurements with a $B_{12}$ initially $\geq$ 1000 ng/l and a solid cancer diagnosed between the measurements. Patients were included in the Curative or Supportive group according to their treatments.

Results: $B_{12}$ changes over time differed between groups ($p = 0.001$): +157.4 ng/l/month in the Supportive care group versus –171.6 ng/l/month in the Curative care group.

Conclusions: The decrease of plasma $B_{12}$ in cases of curative care could suggest that this $B_{12}$ elevation is secondary to solid cancers.

Key words: vitamin $B_{12}$, neoplasms, neoplasm metastasis, antineoplastic agents.

The association between solid cancers and elevated level of total plasma vitamin $B_{12}$ ($B_{12}$) has been demonstrated [1, 2] and remains after adjustment for other causes of elevated $B_{12}$ [3]. However, the design of previous studies did not allow them to clearly determine whether solid cancers were the cause of the $B_{12}$ elevation or vice versa. The $B_{12}$ elevation could be related to cancer through the tumor mass or by means of the granulocytic immune response [4–6]. However, several authors consider that the $B_{12}$ elevation could favor the onset of cancer, due to the role of vitamin $B_{12}$ in cell proliferation [7, 8]. This hypothesis is contradictory to the short-term association observed in cohort studies [1, 2]. The change of $B_{12}$ during the treatment of solid cancers may help explain the direction of this causal relation. Indeed, a decrease of $B_{12}$ after curative cancer treatment would bring an argument for asserting that the cancer induced the $B_{12}$ elevation, directly or indirectly.

In the present study, we compared the change of plasma $B_{12}$ after curative versus supportive treatments for solid cancer in patients with initially elevated $B_{12}$ levels that were related to solid cancers.

Methods. Ethics. The bioethical committee of Angers University Hospital approved this study (n°2019/105) and waived the need for patient consent for this observational study.

Study population. We included patients aged 18 years and over who had been admitted to Angers University Hospital between January 2007...
and May 2015. Patients were required to have undergone two \( B_{12} \) measurements at two different times (T1 and T2), at least 7 days apart.

Patients were included in cases of both i) an elevated level of \( B_{12} \) at T1 defined as \( \geq 1000 \text{ ng/l} \) [3], and ii) a solid cancer diagnosed between T1 and T2. Patients with an active solid cancer already known before T1 or diagnosed after T2 were not included. T1 needed to be performed in the preceding 3 months before the solid cancer diagnosis, and T2 within the next 6 months after the cancer diagnosis. In cases where there were more than two \( B_{12} \) measurements in the period of interest, T2 was considered to be the measurement furthest from T1 in the 6 months following the cancer diagnosis.

We excluded patients presenting other elevated \( B_{12} \)-related diseases previously known or diagnosed during the follow-up: acute liver disease (elevation of transaminases to more than 2 times normal) or chronic liver disease (dysmorphic ultrasound appearance, persistent signs of hepatocellular insufficiency, histology suggestive of cirrhosis), severe chronic renal failure (modification of diet in renal disease (MDRD) creatinine clearance \( \leq 30 \text{ ml/min/1.73 m}^2 \)), autoimmune or inflammatory disease, and myeloid blood malignancy [3–5]. Patients with pernicious anemia or \( B_{12} \) supplementation were also excluded. Assays performed in intensive care and maternity units were excluded because of the metabolic changes observed in these patients [9, 10].

**Total plasma vitamin \( B_{12} \) assay.** \( B_{12} \) measurement was centralized in the biochemistry laboratory of Angers University Hospital. Plasma vitamin \( B_{12} \) was identified using competitive immunoassays with direct chemiluminescence on the ADVIA Centaur system (Siemens Healthcare Diagnostics Inc. Tarrytown, NY 10591-5097 USA). The normal reference range was 200–999 ng/l and the coefficient of variation was 1.3–4.1%.

**Composition of groups.** Patients receiving a curative treatment for solid cancer (chemotherapy, radiotherapy, hormonotherapy and/or surgery) constituted the Curative care group, regardless of the efficacy of their treatment. Patients receiving only supportive care, analgesics or other symptomatic treatments represented the Supportive care group. Patients receiving only minor palliative surgery, symptomatic radiotherapy, or a systemic corticosteroid therapy were excluded because of their potential minor curative effects.

**Statistical analysis.** The quantitative data were presented as medians and quartiles and compared using the \( t \)-test, as the variables demonstrated a normal distribution according to the Kolmogorov-Smirnov test. The qualitative data were presented as absolute values and percent-
| Age  | Sex | Site of primary cancer | Site of metastasis               | Delay from T1 to cancer diagnosis [days] | Vitamin B12 at T1 [ng/l] | Delay from cancer diagnosis to T2 [days] | Vitamin B12 at T2 [ng/l] | Curative treatment before T2 | Delay from cancer diagnosis to treatment [days] | Delay from treatment to T2 [days] |
|------|-----|------------------------|----------------------------------|------------------------------------------|-------------------------|------------------------------------------|-------------------------|--------------------------------|-----------------------------------|--------------------------|
| 69 M | Lungs | Bones | 7 | 1136 | 60 | 1807 | None | NA | NA |
| 71 M | Lungs | Lungs, lymph nodes, bones | 7 | 1422 | 97 | 1805 | None | NA | NA |
| 73 W | Unknown | Lymph nodes | 5 | 1029 | 29 | 1568 | None | NA | NA |
| 76 W | Breast | Bones | 10 | 1307 | 65 | 1228 | None | NA | NA |
| 80 W | Pancreas | Liver, peritoneum | 6 | 1441 | 35 | 2001 | None | NA | NA |
| 81 W | Pancreas | Lymph nodes | 1 | 1150 | 15 | 1613 | None | NA | NA |
| 90 W | Stomach | – | 19 | 1310 | 42 | 1204 | None | NA | NA |
| 91 M | Urothelium | – | 3 | 2001 | 2001 | None | NA | NA | NA |
| 63 M | Pancreas | Lungs | 1 | 1151 | 27 | 1230 | None | NA | NA |
| 58 M | Liver | Liver | 62 | 1032 | 96 | 563 | None | NA | NA |
| 64 W | Ovaries | Peritoneum | 50 | 1578 | 181 | 1179 | Surgery, chemotherapy | 31 | 150 |
| 68 M | Lungs | Bones | 6 | 2001 | 91 | 1044 | Chemotherapy | 6 | 85 |
| 88 M | Prostate | Bones | 26 | 1567 | 93 | 2001 | Hormonotherapy | 14 | 79 |
| 48 M | Colon | Lungs | 6 | 1221 | 7 | 733 | Surgery | 0 | 7 |
| 56 M | Lungs | Bones, lungs, adrenal glands | 7 | 2001 | 107 | 310 | Chemotherapy | 11 | 96 |
| 58 W | Breast | Brain | 11 | 1182 | 77 | 402 | Chemotherapy | 11 | 66 |
| 72 W | Stomach | – | 29 | 1115 | 78 | 666 | Surgery | 0 | 78 |
| 74 W | Esophagus | – | 1 | 1168 | 73 | 673 | Chemotherapy, radiotherapy | 35 | 38 |
| 74 M | Esophagus | Lymph nodes | 20 | 1742 | 38 | 933 | Chemotherapy | 24 | 14 |
this biological abnormality decreased in the first weeks following the initiation of a curative treatment [11]. Our results are in line with the study of Wakatsuki et al., who observed a decrease in \(B_{12}\) levels after surgical excision of gastric cancers. However, this study was restricted to surgical treatment in gastric cancer. Moreover, these results need to be interpreted with caution because gastric surgical procedures might have modified the results need to be interpreted with caution because the intra-subject variations of the absorption of vitamin \(B_{12}\) [12].

In conclusion, the \(B_{12}\) level decreased during curative treatment in solid cancers associated with elevated \(B_{12}\) at the time of diagnosis. This represents an argument for considering this \(B_{12}\) elevation as secondary to solid cancers rather than an underlying condition that favors their onset or progression.

**Conflict of interest**

The authors declare no conflict of interest.

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