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

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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 ≥ 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 ≥ 1000 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 ≤ 30 ml/min/1.73 m²), 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 percentages and compared using Fisher's exact test. To summarize the evolution of plasma B_{12} over time, the best fitting model was selected according to the least squares method. Changes in B_{12} over time were studied using linear modeling (straight line model) after checking for the normality of the distribution of residuals (graphically and with the Kolmogorov-Smirnov test) and the linear distribution with Runs test. Slopes were compared with the F test. The type I error was set at 5%.

The analyses were carried out using GraphPad Prism v6.01 software (GraphPad Software, Inc., La Jolla, CA 92037 USA).

Results. During the study period, 896 patients had at least two B_{12} measurements with B_{12} ≥ 1000 ng/l at T1, including 448 patients without any previously known solid cancer or other elevated-B_{12}-related cause. A cancer was diagnosed between T1 and T2 in 39/448 patients. After excluding patients with other elevated-B_{12}-related diseases diagnosed during follow-up (n = 5, all had chronic liver disease), and patients out of delays for T1 or T2 (n = 15), we included 19 patients for analyses.

9/19 patients received curative cancer treatment between T1 and T2 and constituted the Curative care group, while 10/19 patients received only supportive care and represented the Supportive care group (Table I).

The Supportive and Curative care groups did not differ according to age (74.5 (67.5–83.3) and 68.0 (57.0–74.0) years respectively, p = 0.14), gender (5/10 and 5/9 men respectively, p > 0.99), or B_{12} level at T1 (1229 (1110–1427) and 1567 (1175–1872) ng/l respectively, p = 0.16).

The change of B_{12} over time differed between groups (p = 0.001, Figure 1): B_{12} levels increased in the Supportive care group (+157.4 ng/l/month) and decreased in the Curative care group (–171.6 ng/l/month).

Discussion. Previous studies have demonstrated an association between solid cancers and elevated B_{12} level [1–3]. The short-term association observed in cohort studies suggested that the B_{12} elevation could be due to the cancer, but these studies failed to draw clear conclusions about the direction in which the two are causally connected. In this study, we demonstrated that B_{12} levels decreased during the curative treatment of solid cancers compared to supportive care. This represents an argument for considering that the elevation of B_{12} was directly or indirectly linked to the presence of the solid cancer.

Some authors hypothesized that elevated B_{12} is an underlying condition leading to cancer onset and/or progression [7, 8]. However, our results seemed in favor of the other hypothesis, which attributes an inducing role to the solid cancer, as

Table I. Characteristics of patients

Age [years]	Sex	Site of primary cancer	Site of metastasis	Delay from T1 to cancer diagnosis [days]	Vitamin B_{12} at T1 [ng/l]	Delay from cancer diagnosis to T2 [days]	Vitamin B_{12} 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	6	1805	None	NA	NA
73	W	Unknown	Lymph nodes	5	1029	97	1228	None	NA	NA
76	W	Breast	Bones	10	1307	29	1568	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	4	2001	None	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

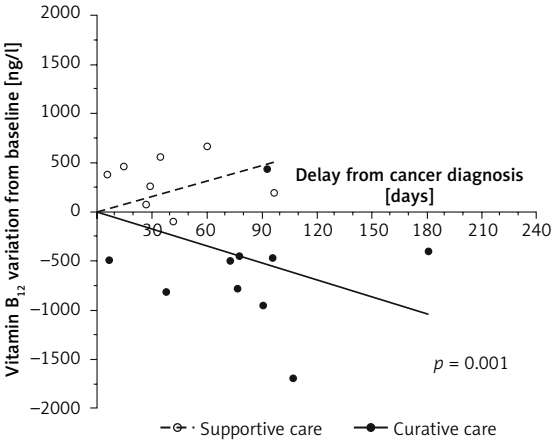

Figure 1. Plasma vitamin B_{12} variation from baseline (T1) in the two groups. Vitamin B_{12} changes over time were studied using linear modeling and the slopes were compared using the *F* test. The *p*-value referred to the comparison of the 2 curve slopes

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 absorption of vitamin B_{12} [12].

The decrease in B_{12} levels after curative treatment of cancer led to the hypothesis that the B_{12} level depended on the tumor mass or replication capacity. Both the higher frequency of elevated B_{12} levels in metastatic cancers [3] and the worst prognosis of cancers associated with elevated B_{12} [3, 6] supported this hypothesis. The mechanism of elevated B_{12} in cases of solid cancer is poorly understood. This may be related to the secretion of a mediator increasing the bioavailability of vitamin B_{12} or to the release of haptocorrins by the granulocytic cells involved in the anti-tumor response [13].

Our study has some limitations. First, the number of subjects is limited. However, the difference of evolution according to the type of treatment is such that our results were significant even with a limited population. Changes in B_{12} must be interpreted with the intra-subject variations of the plasma vitamin B_{12} measurements in mind, but this variation should be similar in both groups [14]. The low number of subjects prevents us from assessing the B_{12} change according to the efficacy of the curative treatments. Another limitation is the retrospective data collection resulting in heterogeneous delay between T1 and T2, whereas a prospective method would allow time points to be standardized. In order to obtain a homogeneous population, we restricted the period of interest of B_{12} measurements. As the B_{12} level may increase in the absence of curative care, we restricted the time from T1 to the cancer diagnosis to allow the B_{12} level at T1 to be approximately equal to the B_{12} level at the cancer diagnosis. We also restricted the time from the cancer diagnosis to T2 to limit the risk of relapses, which might modify the interpretation of B_{12} at T2. We only evaluated the routinely used global assay for vitamin B_{12}, which corresponds to the sum of cobalamin and transcobalamins. However, some authors hypothesized that mainly transcobalamin I was elevated in the solid cancer condition [12]. Lastly, our results suggested that the B_{12} elevation might be secondary to cancers, but the study design did not allow us to assess a causal link.

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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