Pemetrexed, Vitamin B12, and Thoracic Tumors: The Times, They Are A-Changin’

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Abstract

The administration of pemetrexed requires routine supplementation with vitamin B12 and folate, even if blood concentrations are normal, in order to mitigate its hematologic toxicity. Emerging data suggest that such premedication can be initiated less than 1 week before starting chemotherapy. The current available data on later administration of vitamin B12 in patients with thoracic tumors are placed into a general context, and the possible role of such strategy in the era of immunooncology is discussed.
Keywords
Adverse events; Folate; Malignant pleural mesothelioma; Non-small-cell lung cancer; Vitamin supplementation

Introduction
Pemetrexed is a potent antifolate whose primary targets are thymidylate synthase along with dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. Given its activity and the mild toxicity profile, pemetrexed is the preferred platinum partner for the first-line treatment of advanced nonsquamous (NS), non–small-cell lung cancer (NSCLC) without programmed death ligand 1 (PD-L1) high expression (≥ 50%), or oncogene addiction and could be used as a single agent in the second-line setting. Pemetrexed combined with a platinum agent is also the standard of care for the systemic treatment of malignant pleural mesothelioma (MPM).

Vitamin Supplementation and Pemetrexed Safety
After the early observation that a 50% lethal dose of pemetrexed is 60- to 250-fold lower in folate-depleted mice compared to mice fed a normal diet, and after baseline plasma homocysteine levels (a marker of both folic acid and vitamin B12 deficiency) and grade 4 toxicities in patients receiving pemetrexed in a phase 2 study were correlated, supplementation with vitamin B12 and folic acid was implemented into clinical trials with the aim of reducing such adverse events. The comparison between patients receiving vitamin B12 (1000 μg intramuscularly every 9 weeks) and folic acid (350 to 1000 μg daily throughout treatment) and those not receiving supplementation or those receiving only partial supplementation was made in MPM patients recruited in a phase 3 trial comparing cisplatin plus pemetrexed versus cisplatin. Such analysis showed that the rate of grade 3/4 neutropenia was significantly lower in the supplemented group (23.3% vs. 41.4%, P = .011). Furthermore, a previously performed phase 2 study in MPM patients treated with pemetrexed as a single agent showed that those receiving vitamin supplementation experienced less toxicity with a significantly higher median number of treatment cycles administered (6 vs. 2). Moreover, this group had a 5-month greater overall survival (overall survival; 13 vs. 8 months). The supportive evidence generated in these studies led to the inclusion in the pemetrexed label of the mandatory recommendation to start vitamin supplementation at least 7 days before the first cycle of chemotherapy. However, vitamin B12 absorption and distribution after intramuscular administration are reported to be rapid, with plateau levels reached within 24 hours.

Yet in daily clinical practice, a significant proportion of highly symptomatic patients with greatly advanced disease may require prompt treatment initiation for symptom palliation.
The work of Schlei et al.\textsuperscript{12} fits into this scenario. This retrospective single-institution study suggested that same-day vitamin B12 administration is safe in patients receiving pemetrexed-based chemotherapy. The authors analyzed a cohort of 281 newly diagnosed lung adenocarcinoma or MPM patients who received either vitamin B12 (1000 μg intramuscularly, then every 3 cycles thereafter) ≥ 1 day or more before the first cycle of chemotherapy (median 7 days) (group B, 144 subjects) or same-day supplementation (group A, 137 subjects). Treatment regimens comprised cisplatin plus pemetrexed, carboplatin plus pemetrexed, or pemetrexed alone. Fewer patients received single-agent pemetrexed in group A versus group B (13 vs. 26, respectively). No differences in hematologic toxicity from cycle 1 to cycle 2 or from cycle 2 to cycle 3 (primary end point) were observed, although a statistically significant higher number of delays occurred between cycle 2 and cycle 3 in the same-day supplementation arm, mainly as a result of patient preferences. Moreover, the authors did not show a significant difference in the incidence of adverse events requiring supportive care, such as transfusions or antibiotics for neutropenic fever.

The recently presented results of the open-label prospective randomized trial PEMVITASTART\textsuperscript{13} support the conclusion of Schlei et al. In this study, 161 Indian patients with stage III/IV NS-NSCLC were randomized to receive vitamin B12 (1000 μg intramuscularly every 3 weeks) and folic acid (1000 μg orally daily) supplementation 5 to 7 days before treatment initiation or simultaneously (within 24 hours). Pemetrexed was combined with either cisplatin (65 mg/m\textsuperscript{2}) or carboplatin (area under the curve 5) for up to 6 cycles. Among the 150 patients with evaluable data, only the incidence of thrombocytopenia (any grade; 31.2% vs. 16.4%, \(P = .04\)) and the use of erythropoiesis-stimulating agents (22.1% vs. 12.3%, \(P = .03\)) were significantly more frequent in the experimental arm.

Another prospective, phase 2, single-arm, open-label trial performed by Takagi et al.\textsuperscript{11} showed that vitamin B12 administration (1000 μg intramuscularly) 24 to 48 before receiving pemetrexed was not associated with a higher rate of grade 3 or higher hematologic or nonhematologic adverse events compared to historical data with a standard supplementation schedule.

Taken together, these data suggest that in selected clinical situations, clinicians may initiate pemetrexed-based chemotherapy shortly after vitamin supplementation, even if some caution notes should be kept in patients with low bone marrow reserves.

A Changing Landscape: Vitamin B12 Supplementation in the Era of Immunotherapy

With the advent of targeted therapies and immune checkpoint inhibitors (IOs), treatment paradigms in thoracic oncology are rapidly changing. However, chemotherapy is still far from vanishing, as it represents, alone or in combination with IOs, the reference treatment for many patients with NSCLC as well as for those with MPM.

By blocking the interaction between programmed cell death 1 (PD-1; expressed on immune cells such as T lymphocytes) and its ligands (PD-L1 and PD-L2, expressed on cancer cells and some tumor-infiltrating immune cells), monoclonal antibodies directed against PD-1 and...
PD-L1 aim at restoring T-cell activity against tumor cells.\textsuperscript{14} IOs demonstrated their superiority over docetaxel in phase 3 trials in platinum-pretreated patients with advanced NSCLC.\textsuperscript{15, 16, 17, 18, 19} Moreover, pembrolizumab (an anti–PD-1 monoclonal antibody) showed its superiority over platinum doublet in patients with chemotherapy-naive advanced NSCLC with high tumor PD-L1 expression (≥ 50%) in a randomized phase 3 trial (KEYNOTE 024), thus becoming the standard of care in this population.\textsuperscript{19}

Recent results from a phase 3 trial in NS-NSCLC comparing platinum and pemetrexed first-line chemotherapy with pembrolizumab or placebo followed by maintenance with pembrolizumab and pemetrexed in the experimental arm and pemetrexed plus placebo in the control arm showed a significant increase of both overall survival (hazard ratio = 0.49; 95% CI, 0.38-0.64; \(P < .00001\)) and progression-free survival (hazard ratio = 0.52; 95% CI, 0.43-0.64; \(P < .00001\)) in favor of the experimental arm.\textsuperscript{20} This trial included treatment-naive advanced NS-NSCLC patients independent of PD-L1 expression, which was different from the KEYNOTE 024. Vitamin supplementation was prescribed according to the label before initiating chemotherapy and was continued during the pemetrexed and pembrolizumab maintenance period.

In addition to the already discussed role on toxicity prevention, it would be of interest to appropriately investigate a possible role of vitamin B12 and folic acid supplementation on IOs efficacy. Indeed, preclinical and clinical data suggest that vitamin B12 and folic acid deficiencies impair immune system activation, while restoring normal levels may increase natural killer cell cytotoxicity and CD8\textsuperscript{+} lymphocyte activity.\textsuperscript{21} Folate deficiency, for instance, modulates immunocompetence by reducing the proportion of circulating T lymphocytes and their proliferation, especially CD8\textsuperscript{+}.\textsuperscript{22} A study in subjects with vitamin B12 deficiency showed a significant decrease in lymphocytes number and CD8\textsuperscript{+} cells, an abnormally high CD4\textsuperscript{+}/CD8\textsuperscript{+} ratio, and suppressed natural killer cell activity. Of note, supplementation with vitamin B12 reversed these effects, suggesting a potential immunomodulatory role.\textsuperscript{23}

To what extent these data may apply to cancer patients is still unknown, but recent data on gut microbiome composition and immune IO activity showed that new, unexpected players may contribute relevantly in tumor–immune system–host interactions.\textsuperscript{24} We hope that well-designed mechanistic studies will explore the role of vitamin supplementation in the immune landscape.

Conclusion

Vitamin B12 and folic acid supplementation reduce the incidence of grade 3/4 hematologic adverse events in patients treated with pemetrexed. Recent data suggest that vitamin B12 administration less than 7 days before starting chemotherapy could be considered in patients requiring prompt treatment initiation. Beside its protective activity, vitamin supplementation may acquire new, interesting roles in the era of cancer immunotherapy.

Disclosure
The authors have stated that they have no conflict of interest.

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