Bamlanivimab + Etesevimab Therapy Induces SARS-CoV-2 Immune Escape Mutations and Secondary Clinical Deterioration in COVID-19 Patients with B-cell Malignancies

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Bamlanivimab and etesevimab are IgG1 monoclonal antibodies (mAbs) that bind to SARS-CoV-2 spike receptor-binding domain. Treatment with bamlanivimab 2800 mg and etesevimab 2800 mg has been shown to significantly reduce SARS-CoV-2 viral load at day 11 in mild to moderate COVID-19 patients.[1] In the phase III part of the BLAZE-1 trial, the risk of COVID-related hospitalization or death was reduced by 70% in patients treated with this combination versus placebo.[2]

Subsequently, a temporary use authorization for bamlanivimab 700 mg and etesevimab 1400 mg was approved in France to treat patients presenting with high risk of developing severe COVID-19 infection.

Therefore, we treated 34 cancer patients presenting with a mild to moderate form of SARS-CoV-2 infection and no need for oxygen therapy, within 5 days of their first symptoms, with bamlanivimab 700 mg plus etesevimab 1400 mg. Median age was 62.5 (31-83) years old. Most patients presented with a solid tumor ($n = 24$, 71%); 10 (29%) had hematological malignancies and 47.1% were receiving chemotherapy.

COVID-19 outcomes were mostly favorable with supplemental oxygenation required in only 29% of patients versus 41% in our historical cohort (unpublished data). Two patients died of COVID-19 pneumonia but were afterwards found out to be infected by variants with the spike E484K mutation. These favorable issues were correlated with increasing cycle threshold of nasopharyngeal PCR over time (Figure 1).

Strikingly, we noticed that patients with B-cell malignancies ($n = 5$, 15%) displayed a worse clinical evolution, with delayed COVID-19 symptoms from day 14 to day 30 following the mAbs therapy. All of them needed to be hospitalized again after day 14. We carried out viral spike gene sequencing on pre-and post-bitherapy nasopharyngeal swabs. Four of these five patients acquired a mutation in the receptor binding domain: three had a Q493R mutation and one had a E484D mutation. Those five patients were rescued with convalescent plasma therapy: four patients recovered and were subsequently discharged, and one died from COVID-19.

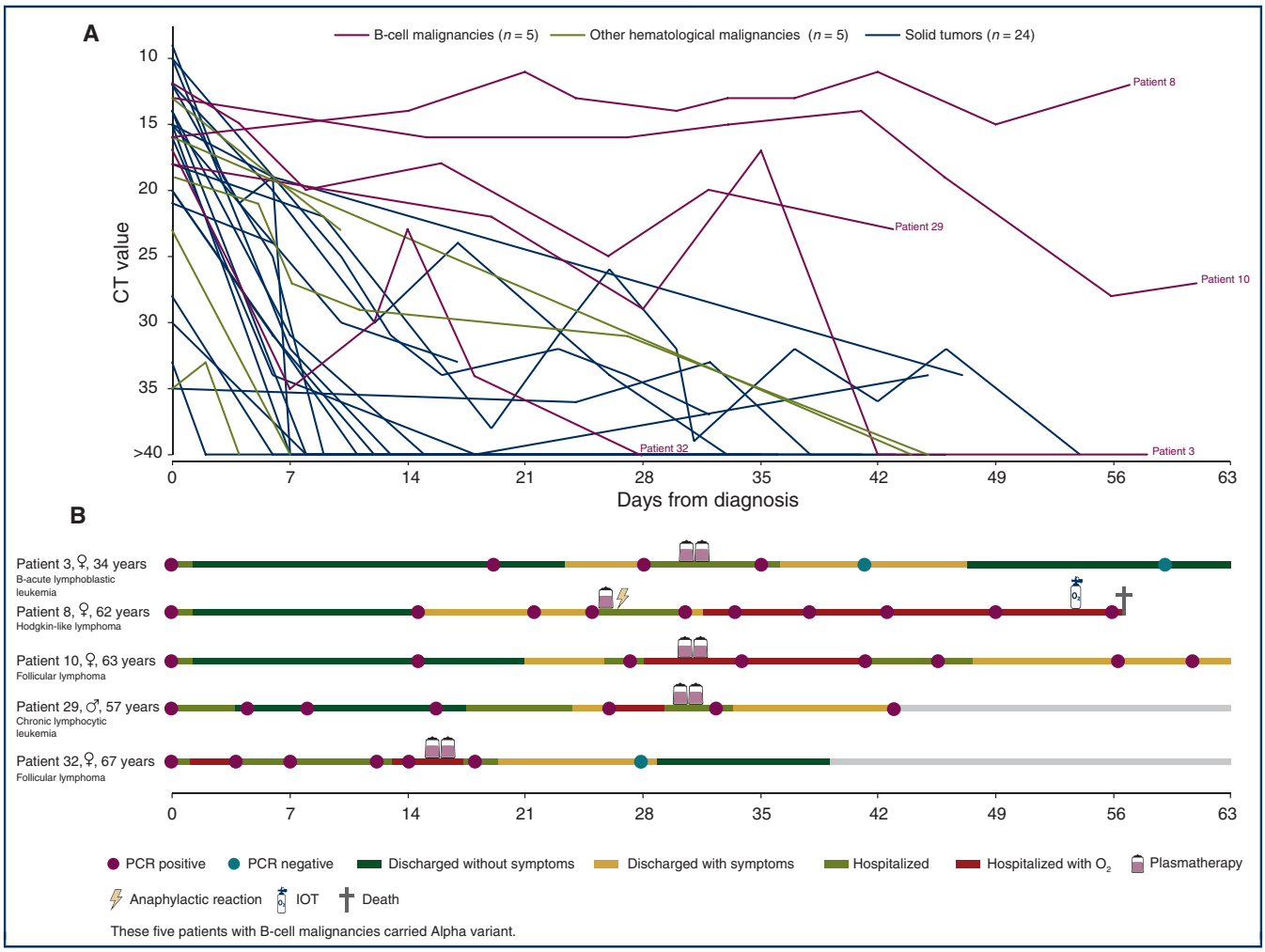

Figure 1. CT and clinical evolution in patients according to cancer type.
CT, cycle threshold; IOT, orotracheal intubation.

Patients with hematological malignancies are at high risk of developing severe COVID-19, due to the inherent immune defect caused by the disease and therapy. In a meta-analysis including 3377 hematological malignancy patients, the risk of death among adult patients was 34% (95% CI, 28% to 39%; $n = 3240$).[3] Also, CD8+ T cells might play a key role in COVID-19 patients with impaired humoral immunity.[4]

Lohr and colleagues reported the emergence of E484K and Q493R mutations after bamlanivimab monotherapy in an immunocompromised patient with the Alpha variant.[5]

In the Gottlieb study, putative treatment-emergent variants were detected in 1% of the patients (1/102) in the bamlanivimab and etesevimab combination group, and in 4.8% of the patients (7/145) in the placebo group.[1] Our data shows that this risk could be much higher in patients with B-cell malignancies.

Blunting viral replication might be sufficient to avoid severe complications in immunocompetent patients, as the mAbs may initiate host immune response.[6]

Patients with impaired humoral and cellular immune response may have prolonged viral replication and higher viral load.[7] Thus, pre-existing viral strains with escaping mAb-neutralization mutation could be selected. Higher doses of IgG1 mAbs, polyclonal antibodies or a combination of several mAbs should be interesting in such B-depleted patients.

Finally, while bamlanivimab 700 mg associated with etesevimab 1400 mg is effective in patients with solid tumors, patients with B-cell malignancies present a secondary clinical deterioration associated with immune escape mutations. Our observation highlights the importance of clinical trials in this specific population, including comprehensive clinical and virological follow-up.

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Significant response of medullary thyroid cancer choroidal metastases to highly selective *RET* inhibitor selpercatinib: a case report

A 53-year-old man was affected by a sporadic metastatic medullary thyroid cancer (MTC), widespread to cervical and mediastinal lymph nodes, lungs, liver, and cerebellum. Over the 10 years from the initial diagnosis, the patient was treated with two tyrosine kinase inhibitors (TKIs) (i.e. vandetanib and lenvatinib off-label). After 1 year from surgery (total thyroidectomy with lymph node dissection of central and left latero-cervical compartment), the patient experienced progression of disease according to RECIST 1.1[1]; therefore, treatment with vandetanib (300 mg/daily, orally) was started in 2012. The patient showed a partial response of the disease, with manageable adverse events, primarily grade 1 and 2 according to Common Terminology Criteria for Adverse Events (CTCAE v. 4.0),[2] and no reduction of dose over time. After 5 years of treatment, progression according to RECIST criteria was shown and treatment with lenvatinib off-label at an initial dose of 24 mg/daily orally was started. Disease remained stable for about 2 years until cerebellar metastases appeared.

Whole brain radiotherapy was carried out with stabilization of the cerebellar metastases and absence of neurological symptoms. However, after 3 years from the beginning of lenvatinib, progression of the disease in lymph nodes and liver metastases was observed, associated with worsening of symptoms (grade 3 fatigue, grade 2 diarrhea, and grade 3 weight loss, according to CTCAE). Moreover, he experienced sudden and complete loss of vision in his left eye. Optical coherence tomography (OCT) and fluorescein angiography showed bilateral choroidal metastases with exudate in the left macular field, responsible for the visual loss (Figure 1A_1 and B_1).

MTC is a neuroendocrine tumor arising from thyroid C cells. About 10% of cases have distant metastases at diagnosis, and about 15% develop distant metastatic disease during follow-up. The metastatic sites are predominately in the liver, lung, bone, and brain, but they can infrequently occur in other sites such as adrenal glands, ovary, pancreas, eyes, and breast. The presence of distant metastases severely worsens MTC prognosis, which drops to a 5-year survival rate of 25% from diagnosis.[3]

To our knowledge, choroidal metastases are extremely rare and have been described in the literature in only nine MTC patients[4,5] (five sporadic and four hereditary cases). The choroid is the vascular membrane of the eye and is the most frequent site of metastases among the ocular structures. The presence of fenestrated endothelium in the highly vascularized choriocapillaris leads to high permeability and may allow both the process of metastasization and the rapid entry of drugs from the blood. At variance with the retina, the metastatic cells do not have to cross the blood—retinal barrier, part of the blood—brain barrier, to reach the choroid. For this reason, the agent does not need to be a central nervous system (CNS) penetrant drug to be effective on the choroidal metastases.

Choroidal metastases have a severe impact on quality of life since they can progress to vision loss. To date, no effective therapies have been reported, and their presence has been associated with a rapid poor prognosis, with <9 months' survival in described cases.[4]

In cases of progressive metastatic MTC, systemic treatments with TKIs are largely employed.[6,7] However, several clinical experiences demonstrated that a mechanism of resistance to the drug develops, and patients on TKI treatment have disease progression.