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Peptide Receptor Radionuclide Therapy (PRRT) during the COVID-19 pandemic: are there any concerns?

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The novel Coronavirus disease 2019 (COVID-19) is now considered a pandemic imposing a tremendous challenge on many nuclear medicine departments. Whereas preliminary precautions have been addressed regarding the risk of infection (*1*) the potential impact of COVID-19 on the risk-benefit ratio of nuclear medicine treatments remains unknown. Here, we discuss risk factors for COVID-19 severity with regard to peptide receptor radionuclide therapy (PRRT), focusing on the question of whether lymphopenia increases risk of infection-related morbidity.

PRRT-associated lymphopenia is a well established side effect. Grade 3-4 lymphopenia occurs in 75% of patients treated with ^{90}Y-DOTATOC (*2*), and 18-52% of patients treated with ^{177}Lu-DOTATATE (*3,4*), with an early nadir 15 days after therapy and subsequent slow partial recovery. Toxicity seems greater after ^{90}Y-peptides and appears to be cumulative (*5*).

The sole study evaluating the impact of PRRT on lymphocyte subpopulations (*5*) indicated that B-cells are predominantly depleted (median 67% reduction): worse with ^{90}Y-DOTATOC (97%) than^{177}Lu-DOTATATE (49%). The prolonged decrease in B-lymphocytes improved in the inter-cycle period and exhibited partial recovery 3 months after the last cycle. T-lymphocytes were less affected (median 31% reduction), and NK cells only marginally decreased (minimally below lower limits in two patients). This explains the lack of severe T- or B-cell related diseases or other opportunistic infections following PRRT. Other innate immunity cells, e.g. macrophages, were not assessed.

The phosphorylated histone variant H2AX (γ-H2AX) is a molecular marker of DNA double-strand breaks, used to estimate the biological dose of irradiation. Post-PRRT lymphopenia seems to correlate with the blood/bone marrow dose, as documented by the increase in γ-H2AX foci in lymphocytes in all treated patients. The peak number of foci correlates with the absorbed dose to tumor and bone marrow and the extent of peripheral blood lymphocyte reduction (*6*).

Data emerging from affected countries indicate that severe forms of COVID-19 are associated with profound laboratory alterations including lymphopenia, thrombocytopenia, and elevated D-dimer, IL-2R, IL-6, IL-10 and TNF-α (*7,8*).

The first study to characterize peripheral lymphocyte subpopulations affected by SARS-CoV-2 demonstrated that all subtypes were involved (CD4-T, CD8-T, B and NK

cells), but a subsequent study showed that CD8-T cell numbers were primarily reduced (*9*). Recovery was associated with an increase in CD8-T and B cells (*10*).

Since lymphopenia is associated with a poor prognosis in the setting of COVID-19, use of procedures with the potential for further immunological compromise and additional lymphopenia, such as extracorporeal membrane oxygenation, sometimes used during respiratory failure, has been regarded with caution (*11*).

At this time, it is not known if the moderately compromised immune response (predominantly involving B-lymphocytes) associated with PRRT results in an impaired capacity to defend against subsequent SARS-CoV-2. Despite the demonstrated neutralizing potential of plasma antibodies (*12*), initial evidence in the development of severe COVID-19 seems to point to a more crucial role for T cells (CD8 and CD4), which are the predominant cells eliminating virus from infected tissue during COVID-19, although they might be involved in organ damage in the later phases of severe infection (*13*).

Consequently, there is no clear theoretical indication that PRRT places patients at significantly greater risk of acquiring COVID-19 or developing more severe infection-related complications. Anectodal experiences among the authors suggest that PRRT-treated patients are not overly represented among our COVID-19 (+) patients.

The potential risks of PRRT in patients with progressive NET during the COVID-19 pandemic need to be considered in the context of the relative risks and benefits of other available therapies. For example, everolimus is immunosuppressive and may increase the risk of infections, including with opportunistic pathogens. The incidence of infections of NET patients treated with everolimus is approximately 20-29% (all grades) and 5-10% for grades 3 and 4 (*14*). Similarly, patients treated with temozolomide are at risk for lymphopenia, although risk of opportunistic infections appears to be significant only with dose-dense regimens and/or with corticosteroids (*15,16*).

Given the slow and low-dose radiation delivery over time, as opposed to high-dose external-beam radiotherapy or chemotherapy, it is hypothesized that PRRT would have no significant impact on the other hallmark of COVID-19, the coagulopathy related to generalized vasculitis, immune thrombocytopenia and disseminated intravascular coagulation (*17,18*).

The kidney is another COVID-19 target, possibly through the ACE2 receptor . Subclinical kidney injury is thought to occur in many COVID-19 patients, severely in about 3% of older subjects, with hypertension (*19*). It is unclear whether the generally subcinical nephrotoxicity produced by prior ^{177}Lu-DOTATATE could constitute an additional risk factor in COVD-19 induced renal injury.

Given the evolving nature of this pandemic and the scarcity of data on the subject, the nuclear medicine community is encouraged to prospectively collect and report information regarding toxicity in patients undergone PRRT, either before or after COVID-19. At this time, however, routinely monitoring lymphocyte subpopulations would only have research value. Considering the expected rarity of the association of PRRT and COVID-19, the authors proposes a registry under the aegis of the dedicated scientific societies to collect such data and specifically evaluate the potential association between radiation-induced toxicity (hematological, renal) and COVID-19.

Although available data are scarce, the authors agree that, for now, PRRT-related lymphopenia does not appear to constitute a strong risk factor for acquiring COVID-19 infection and for developing severe complications. The authors, however, recommend careful vigilance regarding the incidence and clinical course of COVID-19 cases in patients undergoing PRRT and postponing treatment in active COVID-19 infection. Continuous consideration should be given to the risk-benefit ratio of PRRT during this pandemic, accounting for the geographic prevalence of COVID-19 in the patient's area as well as patient frailty and comorbidities which may impact pulmonary and renal complications. Few weeks delay in highly affected areas for individuals with slowly progressing tumors or with severe comorbidities can be considered, while patients with aggressive tumors or those living in scarcely affected areas should receive treatment with no delays.

Disclosure

LB: unpaid consultancy/advisory board: AAA, Ipsen, Curium, Clovis Oncology. Research: AAA.

EB: unpaid advisory board: AAA.

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DF: Steering committee: NETTER 2.

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