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Combination therapy in immunocompromised patients with COVID-19

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BACKGROUND

- Prolonged or relapsed COVID-19 in severely immunocompromised patients still represents a difficult challenge to face in these days.
- Prolonged shedding of viable virus and persistent symptomatic SARS-CoV-2 infection not only increases morbidity and mortality, but also have negative impact on the access to treatments of the underlying malignancy, with lack of remission, relapse, or delayed effective therapeutic options.
- There are currently 2 antiviral drugs who are still effective for treatment COVID-19: remdesivir, an inhibitor of the viral RNA-dependent RNA polymerase; nirmatrelvir, a 3C-like protease inhibitor administered with ritonavir booster.
- Combining antiviral agents with anti-spike monoclonal antibodies (mAbs) can have a potential advantage of higher efficacy due to their different antiviral mechanisms.

METHODS

- This retrospective observational study was conducted from march 2022 to march 2024 and includes 26 immunocompromised hospitalized adults with severe immunodeficiency.
- All patients received dual or triple combination therapy with antivirals remdesivir, nirmatrelvir/ritonavir and mAbs sotrovimab or tixagevimab/cilgavimab
- All patients were followed until the discharge or death during hospitalization.

STUDY POPULATION

- 23 patients have onco-hematological diseases. The other 3 patients respectively have:
  - solid tumor with ongoing chemotherapy;
  - multiple sclerosis with ongoing treatment with anti-CD20 mAbs ocrelizumab,
  - post-transplant immunosuppression.
- In table 1 are summarized the main characteristics of patients enrolled in our study.
- 17 patients were vaccinated with at least 2 doses of SARS-CoV-2 vaccine, and the average time from latest dose was almost a full year.

Table 1: Overall patients' characteristics

Characteristics	N (%)
N. Patients	26
Age, y, median	69
Male (sex)	18 (69)
Underlying disease	
Hematological disease	23 (88)
Non-Hodgkin lymphoma	12 (46)
Acute myeloid leukemia	2 (8)
Chronic lymphocytic leukemia	3 (11)
Chronic myeloid leukemia	1 (4)
Hodgkin lymphoma	1 (4)
Acute Lymphoblastic Leukemia	3 (11)
NK-cell leukemia	1 (4)
Solid tumor	1 (4)
Anti-CD20 treatment	2 (8)
Comorbidities (≥2)	24 (92)
Vaccinated (≥ 2 doses)	17 (65)
Days between hospitalization and latest COVID-19 vaccine dose, median	356
Ventilation with HFNC or NIV	5 (19)

RESULTS

- 6 patients needed a re-treatment during hospitalization or were been already treated for SARS-CoV-2 infection in the last 3 month before the hospitalization.
- All patients after the treatment achieved negativity to nasal-swab for SARS-CoV-2 during the hospitalization. One patient died with COVID-19-related ARDS during hospitalization, the other 25 patients were discharged or, if needed, transferred to another department after the negativization. One of them died due to worsening of his hematological disease after been transferred to the hematology department.
- 7 patients on admission were categorizable as critical COVID-19, the other 19 as severe.
- In table 2 are summarized the combination therapy regimen we used, in particular there are 2 options of triple combination treatments with remdesivir plus nirmatrelvir/ritonavir plus one mAb (either sotrovimab or tixagevimab/cilgavimab).

  Dual combination therapy included association with 2 antivirals (remdesivir + Nirmatrelvir/ritonavir) or 1 antiviral (remdesivir) plus 1 mAb (sotrovimab).
- The duration of treatment administered ranges from a minimum of 3 days to a maximum of 15 days, with a median of 10 days and a standard deviation of 3 days.
- On average, viral clearance was achieved after a median of 21 days (IQR 7.0-96), SD=24 from admission to the hospital.

SAFETY

- No adverse events were reported for every combination regimen we used.
- Both antivirals and mAbs demonstrated a good tolerability profile.

Table 2

Therapy administered and results	N (%)
Critical COVID-19 upon admission	9 (35)
Outcome (recovery)	25 (96)
Deaths COVID-19-related	1 (4)
Needed re-treatment	6 (23)
Triple combo therapy: 2 antivirals + mAbs	11 (42)
Sotrovimab	9 (35)
Tixagevimab/cilgavimab	2 (8)
Dual combination therapy	15 (58)
Sotrovimab + remdesivir	8 (31)
Remdesivir + nirmatrelvir/ritonavir	6 (23)
Days of treatment, median	10
Days of hospitalization before nasal swab negativization, median	21 (7-96)
Adverse events (tolerability)	0

CONCLUSIONS

- Our real-life experience supports the effectiveness of combination therapy with antivirals and/or mAbs even in severely immunodepressed patients affected by COVID-19 who required hospitalization, all patients treated achieved negativity to nasal-swab during the hospitalization.
- No patient progressed to more severe forms of COVID-19 after the treatment, although one patient died during hospitalization from sepsis and ARDS (both present upon admission).
- Both dual and triple combination therapy showed a good tolerability profile.
- In these patients, the rapid start of combination therapies can play a fundamental role in reducing the risk of evolution towards more severe forms of COVID-19.
- On average, the duration of treatment necessary to achieve recovery from COVID-19 for our sample of immunocompromised hospitalized patients was 10 days
- Timely negativization to COVID-19 for these patients it's crucial in order to ensure them access to treatments for the underlying malignancy