COVID-19 vaccines. Version 2.0 December 21, 2020

COVID-19 vaccines have been developed, tested, and approved with an unprecedented speed with the aim to control the pandemic. Two vaccines are currently approved by the FDA for emergency use in the USA (Moderna/National Institutes of Health, Pfizer/BioNTech) both based on mRNA technology. The British competent authority has approved the Pfizer/BioNTech vaccine for use in the UK. The EMA has approved the Pfizer/BioNTech vaccine December 21.

Recently presented information through media reports and press releases suggest that four vaccines have a high efficacy and seem to be safe in immune competent individuals. Information about additional vaccines can be expected. It is recognized that there might be national guidelines that need to be followed about which groups will be prioritized and which vaccines will be used. There are 18 vaccines in phase III trials (New York Times Coronavirus Vaccine Tracker, (https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html). These represent different technologies using either mRNA, adenoviral vectors, the spike protein, or inactivated virus as antigens. For some of these vaccines, the information is still limited. The two in the USA licensed vaccines are based on mRNA technology.

Results from the phase III Pfizer/BioNTech vaccine including 43500 subjects have been published[1]. This showed 94.6% protection after two doses of vaccine given three weeks apart. When results were split by age, the protective efficacy was 94.6% in adults 18 – 65 and 92.9% in adults > 65 years of age. In the phase III study the safety was good. In early clinical use, two anaphylactic reactions occurred in subjects previously having experienced such reactions. The FDA and CDC have presented advice for the use of this vaccine and it is recommended for immunosuppressed patients although no specific data has been presented[2]. It is recognized that

the protection efficacy might be lower in immunosuppressed individuals. More information can be obtained at the FDA (www.fda.gov) and CDC (www.cdc.gov) websites.

The results from the Moderna/National Institute of Health vaccine have not been published. However, in the FDA briefing document at the time of its emergency approval, it is stated that the phase III study included 30400 subjects each receiving two doses of vaccine or placebo given one month apart. The protective efficacy is reported to be 94.1% (95.1% in adults 18 – 65 and 86.4% in adults above the age of 65). No specific safety concerns were identified.

Regarding the as of today non-licensed vaccines, there has been an interim publication of the results with the Astra/Zeneca vaccine pooling results from four randomized trials[3]. This vaccine is based on a replication-deficient chimpanzee adenoviral vector containing the gene for the SARS-CoV-2 spike protein. The primary efficacy endpoint was symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. All participants received two doses 28 days apart. The preliminary analysis included 11600 participants and the overall protective efficacy was 70.4%. One uncertainty with these results is that patients receiving two full doses of the vaccine showed a protective efficacy of 62.1% vs. 90.0% in participants receiving one half dose followed by one full dose. Two other vaccines use similar technology (Johnson & Johnson, Gamaleya Research Institute; Sputnik-V) and the latter is in clinical use in Russia, but no data has been published from the phase III studies with either of these vaccines. There are also different vaccines in limited use in China, with only limited information available. One is based on a replication-deficient viral vector and others on inactivated viral particles.

It is highly unlikely that there will be any data in HCT or CAR T cell treated patients at the time of approval. Thus, a logical vaccination algorithm will have to be developed without definite information.

Neither the mRNA nor the vector-based vaccine technology has been used previously in HCT recipients and it is difficult to deduce if one technique would be more likely to produce a more robust immune response in immunosuppressed individuals or would have different safety profiles. Currently the mRNA vaccines have been deemed safe to use by the CDC/FDA in immunocompromised patients. Regarding the replication-deficient vector vaccines, we will have to wait for formal approval to assess their use in our patient groups. As a general rule, the

vaccines that use SARS live attenuated virus or replicating viral vectored vaccines (vectored by measles, vesicular stomatitis virus, influenza virus, for example) are contraindicated in HSCT or CART-T cell receptors. All these live-attenuated virus or replicating viral vectored vaccines are currently only in phase 1 trials.

Prioritization of HCT or CAR T patients for getting the vaccine will be made by the health authorities in each country. It is our belief that patients early after HCT or CAR T therapy, those on immunosuppression, and those with pulmonary compromise ought to have a high priority together with health care staff caring for these patient groups.

The use of a vaccine for SARS-CoV-2 modifies the interpretation of the serologic test. As the two FDA licensed vaccines (Pfizer/BioNTech, and Moderna/National Institute of Health) induce antibodies against the spike glycoprotein, to evaluate for evidence of infection in an individual vaccinated, a test specifically evaluating IgM/IgG to the nucleocapsid protein should be used.

<u>Currently our assumptions and recommendations are.:</u>

1) HCT patients could be vaccinated with whatever vaccine is made available considering the results of the phase III trials in the healthy population, we can assume that the HCT patient population is among the ones, who should have the highest benefit/risk ratio of the vaccination.
2) This message is important to explain to patients and their relatives.
3) If the transmission rate in the surrounding society is high, vaccination could be initiated at the earliest three months after HCT and take priority over the regular vaccinations program. With the currently approved two-dose vaccines, this means a postponement of approximately 6 – 8 weeks for other vaccines.
4) If transmission in the surrounding society is well controlled, it would be logical to wait until six months after transplantation to initiate vaccination.
5) Studies with other vaccines with good immunogenicity potential have shown efficacy also in patients with ongoing moderately severe GVHD without obvious risks to result in worsening of the GHVD. These patients should therefore not be excluded. Although side effects are expected as with any vaccine, there is no example of a non-live vaccine having more frequent or more severe side effects in HCT recipients than in the healthy population of the same age range.

6) So far, there is no data suggesting immune activation of underlying conditions making the likelihood that COVID-19 vaccines will exacerbate GVHD low.
7) Reasonable exclusion criteria from COVID-19 vaccination based on our current knowledge are:
    a. Severe, uncontrolled acute GVHD grades III – IV.
    b. Recipients, who have received anti-CD20 antibodies such as rituximab during the past six months.
    c. CAR T cell patients with B-cell aplasia earlier than six months after treatment.
    d. Recent therapy with ATG or alemtuzumab.
    e. Children < 16 since there is no information regarding vaccination of this group in any of the studies. It can be justified to vaccinate adolescents ages 16 – 18 years old[4].
8) Studies of safety, efficacy and immunogenicity of COVID-19 vaccines are recommended, but positive antibody testing (both to spike or nucleocapsid proteins) is not equivalent with sufficient protection; and general preventive practices should be continued.
9) Healthcare workers should be vaccinated to protect the patients.
10) House-hold contacts should be vaccinated, especially when the HCT recipient is early after transplant or receiving intensive immunosuppression, as such patients are unlikely to respond to COVID-19 vaccine.
11) The duration of protection is unknown, but it is possible that it will be shorter in immunocompromised patients than in healthy individuals as has been shown with other vaccines[5,6]. Thus, booster doses as most likely needed but it is unclear when such should be given.

Other vaccines: Influenza vaccination is strongly recommended in HCT and CAR T cell treated patients. It is also logical to ensure that the patient's vaccination status against *S. pneumoniae* is up-to-date.

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Table 2

Summary of EBMT RECOMMENDATIONS for SARS-CoV-2 vaccines

General considerations

- **Available vaccines**
  - **Two vaccines are currently approved by the FDA** for emergency use in the USA (Moderna/National Institutes of Health, Pfizer/BioNTech) both based on mRNA technology**. The** British competent authority has approved the Pfizer/BioNTech vaccine for use in the UK. The EMA has approved the Pfizer/BioNTech vaccine December 21.
    - The two in the USA licensed vaccines are based on mRNA technology
- **Regulatory agencies recommendation**
  - **The FDA and CDC have presented advise** for the use of this vaccine and it is recommended for immunosuppressed patients although no specific data has been presented.
  - It is recognized that the protection efficacy might be lower in immunosuppressed individuals.
- **Vaccine data for HCT or CAR T cell treated patients**
  - **It is highly unlikely that there will be any data in HCT or CAR T cell treated patients** at the time of approval. Thus, a logical vaccination algorithm will have to be developed without definite information
  - **Neither the mRNA or the vector-based vaccine technology** has been used previously in HCT recipients and it is difficult to deduce if one technique would be more likely to produce a more robust immune response in immunosuppressed individuals or would have different safety profiles.
- **Prioritization of HCT or CAR T patients for getting the vaccine**
  - It is our belief that patients early after HCT or CAR T therapy, those on immunosuppression, and those with pulmonary compromise ought to have a **high priority** together with health care staff managing these patient groups
- **Other vaccines**
  - **Influenza vaccination** is strongly recommended in HCT and CAR T cell treated patients. It is also logical to ensure that the patient's vaccination status against ***S. pneumoniae*** is up-to-date

Recommendations

1. **HCT patients could be vaccinated with whatever vaccine is made available** considering the results of the phase III trials in the healthy population, we can consider that the HCT patient population is among the ones, who should have the best benefit/risk ratio of the vaccination.
    - This message is important to explain to patients and their relatives.

2. **Moment after HSCT for vaccine administration**
    - **If the transmission rate in the surrounding society is high**, vaccination could be initiated at the earliest **three months after HCT** and take priority over the regular vaccinations program. With the currently approved two dose vaccines, this means a postponement of approximately two months.

    - **If transmission in the surrounding society is well controlled**, it would be logical to wait until **six months after transplantation** to initiate vaccination.

3. **Not exclude HSCT patients with GVHD**

    - Studies with other vaccines with good immunogenicity potential have shown efficacy also in patients with ongoing moderately severe GVHD without obvious risks to result in worsening of the GHVD. These patients should therefore not be excluded. Although side effects are expected as with any vaccine, there is no example that side effects of non-live vaccines be more frequent or more severe in HCT than in the healthy population of the same age range. So far, there is no data suggesting immune activation of underlying conditions making the likelihood that COVID-19 vaccines will exacerbate GVHD low.

4. **Reasonable criteria to postpone vaccination** with our current knowledge are:
    - Severe, uncontrolled acute GVHD grades III – IV.
    - Recipients, who have received anti-CD20 antibodies during the last six months.
    - CAR T cell patients with B-cell aplasia earlier than six months after treatment.
    - Recent therapy with ATG or alemtuzumab.
    - Children < 16 since there is no information regarding vaccination of this group in any of the studies. It can be justifiable to vaccinate adolescents ages 16 – 18 years old.

5. **General preventive practices should be continued after vaccination**
    - Studies of safety, efficacy and immunogenicity of COVID-19 vaccines are recommended, but positive antibody testing (both to spike or nucleocapsid proteins) is not equivalent with sufficient protection; and general preventive practices should be continued.

6. **Healthcare workers should be vaccinated** to protect the patients.

7. **House-hold contacts should be vaccinated,** especially when the HCT recipient is early after transplant or receiving intensive immunosuppression, as such patients are unlikely to respond to COVID-19 vaccine.

8. **The duration of protection is unknown** and it is possible that it will be shorter in immunocompromised patients than in healthy individuals as has been shown with other vaccines. Thus, booster doses as most likely needed but it is unclear when such should be given.