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Current Perspective

Coronavirus disease (COVID-19) outbreak and phase 1 trials: should we consider a specific patient management?

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Abstract The outbreak of the Coronavirus disease (COVID-19) pandemic has deeply challenged healthcare systems and care of patients with cancer. Phase 1 studies are among the most complicated clinical trials and require thorough patient selection, as well as intensive patient monitoring. In this perspective, we discuss the key factors that should be considered for the conduct of phase 1 trials and management of COVID-19–positive patients with cancer enrolled in such trials. We notably present the risks and challenges raised by COVID-19–infected phase 1 patients, in terms of safety, toxicity causality assessment, drug efficacy evaluation and clinical research priorities. We finally propose some guidelines for the conduct of phase 1 trials and management of COVID-19–infected patients in a pandemic time.

1. Introduction

The outbreak of the Coronavirus disease (COVID-19) pandemic has unexpected consequences on all aspects of life, society, economy and healthcare. In oncology, it is now well established that cancer represents a comorbidity that is associated with a higher probability of severe forms of the COVID-19 infection [1,2]. Phase 1 trials, which require an intensive monitoring of patients with multiple visits in in-patient and out-patient units, may represent by themselves an additional major risk of contamination in a pandemic context. Furthermore, the saturation of intensive care units by COVID-19–infected patients adds a significant safety risk for patients with cancer enrolled in phase 1 trials associated with frequent life-threatening complications, such as

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cytokine release syndrome in protocols evaluating CAR-T cells or bispecific antibodies, or for patients undergoing challenging tumour biopsies.

Preliminary guidelines, which are being refined as experience on the COVID-19 infection management increases, have been established for the clinical practice of routine cancer treatments [1,2]. These include postponing adjuvant chemotherapy, limiting dose intensity of chemotherapy or intensifying surveillance in endemic areas and epidemic times. However, no recommendations currently exist on the management of COVID-19–positive patients included in phase 1 trials. Phase 1 trials represent the first evaluation of a drug – or a drug combination – into humans and aim at establishing the optimal dose that can be administered safely and with a maximal efficacy. These trials have therefore some inherent specificities that require specific attention for the management of COVID-19–positive patients.

Here, we propose some elements of thought that may be considered for the conduct of phase 1 trials and management of COVID-19–positive patients with cancer who are candidates for such trials or already enrolled in them. Considering the current absence of clinical data in this field, these reflections are based on our phase 1 experience only and are deemed to evolve and be enriched at a wider and international level to serve for the establishment of evidence-based guidelines.

1.1. Patient safety

Among retrospective studies that have reported series of patients with cancer and COVID-19 infection, the administration of an anticancer agent within 15 days before COVID-19 diagnosis has recurrently been identified as a risk factor for severe complications [1,2]. Several classes of investigational phase 1 drugs could indeed influence the course of the COVID-19 infection. These include not only myelosuppressive agents but also immune therapies – especially those interfering with the lymphoid cell function [3], monocyte function [4] or type I interferon response [5] – and epigenetic therapies (e.g. bromodomaine extra-terminal [BET] inhibitors that impact the haematopoietic cell differentiation and have anti-inflammatory properties [6,7]). Drugs used to treat potential adverse events caused by immune therapies evaluated in phase 1 trial could also interfere with the course of the COVID-19 infection, notably steroids, anti–IL-6 (tocilizumab, also used to treat the COVID-19–induced cytokine storm [8]), anti-tumour necrosis factor therapies or even potentially antibiotics – some of which are currently assessed in dedicated trials for potential therapeutic effects against the COVID-19 infection [9]. Therefore, the phase 1 drug safety profile should be thoroughly considered in the decision of maintaining a COVID-19–positive patient on trial, and the investigational drug should be temporarily or permanently halted in case of any doubt of increased safety risk for the patient.

1.2. Toxicity causality assessment

Two main phases can be distinguished within phase 1 trials. The first one is the dose-escalation phase, where the optimal dose is not yet established; in this phase, toxicities (and their causality) have to be thoroughly monitored and reported at each dose level; also, the dose-limiting toxicity (DLT) period, which usually corresponds to the first cycle of treatment, is of crucial importance, as toxicities observed during this phase will guide the dose-escalation (or dose de-escalation) process. The second phase is the dose expansion phase, which aims at confirming that the dose determined during the dose-escalation phase is adequate. Although the monitoring of adverse events is still very important during this phase, the toxicity profile of the drug is usually, at least in part, already known, which makes the causality assessment of adverse events (AEs) and severe AEs (SAEs) potentially easier.

The screening and management of COVID-19 infection should therefore probably differ between these phases. Traditionally, patients with active severe infections or chronic viral infections (e.g. hepatitis C or HIV) have been excluded from phase 1 trials. We would suggest that any phase 1 candidate is screened for COVID-19 using PCR before starting the experimental treatment and that patients with a positive PCR are subsequently excluded from the trial, even if asymptomatic at the time of diagnosis. Indeed, considering the variety of clinical forms that the COVID-19 infection takes (including gastro-intestinal, cardiac, cutaneous, neurological, olfactive, psychiatric, thromboembolic etc.), we can anticipate that it would be very difficult to precisely establish the aetiology of (S)AEs in patients with an active infection. Even if the presence of a fever – observed in the majority of COVID-19–infected patients– could orientate towards an active infection, this causality establishment would remain extremely challenging for isolated biological findings such as elevated liver, pancreatic, muscle or cardiac enzymes; indeed, such asymptomatic enzyme elevations regularly observed in phase 1 trials are drug related but are most often deemed to be non-clinically significant; by contrast, such biological abnormalities could be important in the context of COVID-19 infection, as they have been reported to be associated with a worse outcome [3]. An inadequate causality assessment during the dose-escalation phase could lead to wrongly halting the drug's dose-escalation phase, which may have deleterious and irreversible consequences for subsequent drug development.

For these reasons, we would recommend screening weekly for COVID-19 PCR during the DLT period and replacing patients who develop a clinical or biological

(i.e. asymptomatic but PCR positive) COVID-19 infection during the DLT period. Beyond the screening phase and the DLT period, we would suggest to perform a regular COVID-19 PCR, for example, at the end of the DLT period and subsequently every four cycles and/or upon clinical symptoms. Patients who develop a COVID-19 infection after the DLT period or during the dose-expansion phase may stay on trial, as long as the treatments received for the management of the COVID-19 infection do not interfere with the phase 1 drug metabolism (pharmacodynamics and pharmacokinetics) or efficacy, and criteria suggested in the following paragraphs are met.

1.3. Efficacy assessment

The COVID-19 infection may also have consequences affecting the phase 1 treatment efficacy. For example, a significant proportion of phase 1 trials currently evaluate novel immune therapies (as monotherapy or as combinations with an anti–PD-(L)1 backbone), whose efficacy relies on the (re-)activation of a cytotoxic T-cell antitumour response. However, a key feature of the COVID-19 infection is lymphocytopenia, which is observed in more than 80% of the patients and whose severity correlates with worse prognosis [1–3]. Although intratumor lymphocytes may be a distinct population from peripheral circulating lymphocytes, we might hypothesise that such profound COVID-19–induced lymphocytopenia may negatively impact on the efficacy of immune therapies aiming at triggering a T-cell–based antitumour response. Similarly, the administration of steroids, such as dexamethasone, to treat severe forms of COVID-19 infections may negatively impact the efficacy of some anticancer immunotherapies [10]. Although theoretical at this stage, such elements should be considered for maintaining a patient on trial and for evaluating phase 1 drugs' efficacy.

1.4. Clinical research priorities

From a regulatory point of view and by law, a patient cannot be included in two different therapeutic interventional trials. Therefore, a patient with cancer that develops a COVID-19 infection could either be included in a phase 1 cancer study or in a COVID-19–related investigational trial. Unless there is a strong rationale for including the patient in a phase 1 trial (e.g. molecular alteration with a matched drug, positivity for a specific efficacy biomarker for a drug administered at the recommended phase 2 dose etc.), the inclusion in a study evaluating treatments against COVID-19 should probably be favoured, especially considering the current pandemic and emergency for identifying efficient therapeutic strategies. Once the COVID-19 infection has resolved, the phase 1 trial could be proposed to the patient. Provisions may be envisioned in future phase 1 cancer protocols to allow the inclusion of such patients earlier than the commonly requested 21-day symptom-free window, as long as blood counts have recovered to levels that are compatible with the trial's inclusion criteria. Indeed, unnecessarily delaying a potentially efficacious anticancer treatment could also impact the long-term prognosis of the patient [11,12].

1.5. COVID-19–positive phase 1 patients management

In case an asymptomatic or non-severe COVID-19 infection is confirmed in a phase 1 patient outside the DLT period, this patient could stay on trial in most cases. However, adjustments should be performed whenever feasible until the patient has recovered clinically and biologically (i.e. presents a negative PCR), after discussion and approval of the trial sponsor, including (i) minor deviations to limit hospital visits (e.g. pooling of laboratory testing, disease evaluations, biopsies, treatment administration and delivery etc.); (ii) teleconsulting at increased frequency with the phase 1 investigator, combined with regular home visits from the patient's local general practitioner and blood tests at a local facility, to thoroughly collect AEs and regularly check for signs of severe COVID-19 infection; (iii) treatment shipping to the patient's domicile; (iv) skipping of some surveillance clinics at the hospital when the patient has been stable and on trial for more than 6 months and does not present any evolving drug-related AE; (v) stronger personal protection for the patient; (vi) active and regular reminder to strictly avoid any self-medication and over-the-counter drugs (notably non-steroidal anti-inflammatory drugs). To limit the risk of COVID-19 infection in phase 1 patients, the patient and its household should also be regularly reminded of strictly respecting the self-protection measures and be provided personal protection equipment whenever needed.

1.6. Clinical experience at the Drug Development Department during the pandemic

COVID-19 outbreak was intense in the Paris region from mid-March to the end of April 2020. From March 14th to April 28th 2020, 178 patients with cancer were managed for COVID-19 at Gustave Roussy Cancer Center. Overall, 125 (70.2%) patients were hospitalised for COVID-19, 47 patients (26.4%) developed clinical worsening and 31 patients (17.4%) died [13].

During that period, the Drug Development Department continued its activity with the following measures: (i) all lung biopsies were cancelled to limit the risk of severe complications such as pneumothorax that would require access to the intensive care unit for pleural drainage or artificial ventilation; (ii) all patients were tested at least at C1D1 using rapid PCR; (iii) visits to the hospital were cancelled whenever feasible and

Table 1
Guidelines for patients with cancer enrolled in phase 1 trials at Gustave Roussy.

Patient status	COVID-19 PCR	COVID-19 serology	Guideline
Asymptomatic	Negative	Negative	Social distancing and mask
	Negative	Positive	Social distancing and mask
	Positive	Negative	Delay unnecessary visits and treatment
Symptomatic	Positive	Negative	Delay or stop phase 1 trials

teleconsultation was favoured, as well as treatment shipment at home, whenever feasible. Recommendations were given to patients, who were managed according to the guidelines presented in Table 1.

Three patients who received bispecific agents and developed a cytokine release syndrome were successfully managed in our ward, in strong interaction with the Gustave Roussy intensive care unit. Rapid PCR tests identified four patients with a COVID-19–positive PCR: one patient in screening for whom cycle 1 day 1 was delayed; one patient in the DLT period, who was maintained on trial as he remained completely asymptomatic and did not develop any AE and two patients at later stages of the phase 1 trial (cycles 10 and 12) who required a treatment delay because of self-isolation. No COVID-19–related deaths occurred.

2. Conclusion and perspectives

General hospitals and clinical trial units have shown a remarkable ability to rapidly adapt their routine practice to the COVID-19 outbreak to be able to treat COVID-19–infected patients while maintaining some other essential activities for patients with life-threatening or severe chronic diseases. Maintaining such activity is indeed absolutely crucial for patients with cancer, for which any treatment delay most often results in a loss of chance and worse outcome [12].

Phase 1 trials are the most resource-consuming and complicated form of clinical trials, from a safety and organisational point of view, as they involve multiple hospital teams (clinical trial unit, pharmacy, interventional radiology etc.), clinical research organisations and drug companies, and require intensive patient monitoring. During the peak of the pandemic in France, we successfully managed to maintain our drug development unit open and to treat patients without any additional delay, while not causing any nosocomial COVID-19 infection. However, treating COVID-19–infected patients in phase 1 trials is not straightforward, and specific precautions, described earlier, should be taken regarding their inclusion and management. The COVID-19 infection could indeed not only influence the patient safety but also have consequences on the drug efficacy and the whole drug development process outcome.

As further waves of the pandemic may re-occur, we need to be prepared and have specific management guidelines ready so that phase 1 trials are minimally disrupted and patients remain optimally treated. We would therefore suggest to create an international registry and taskforce for phase 1 patients infected with COVID-19 infections so that various practices can be compared [14] and consensual guidelines are eventually established.

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Conflict of interest statement

As part of the Drug Development Department (DITEP), S.P.-V. and C.M. report being principal investigators or sub-investigators of clinical trials from Abbvie, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, Astra Zeneca, Aveo, Bayer Healthcare Ag, Bbb Technologies Bv, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Eli Lilly, Exelixis, Forma, Gamamabs, Genentech, Inc., Glaxosmithkline, H3 Biomedicine, Inc, Hoffmann La Roche Ag, Innate Pharma, Iris Servier, Janssen Cilag, Kyowa Kirin Pharm. Dev., Inc., Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, PharmaMar, Pierre Fabre, Roche, Sanofi Aventis, Taiho Pharma, Tesaro Inc and Xencor. S.P.V. reports participating in advisory boards for Merck KGaA and receiving research funding from Merck KGaA, Boehringer Ingelheim and Roche for unrelated research projects. J.-C.S. reports serving as a full-time employee of Medimmune/Astra Zeneca from September 2017 to December 2019; receiving consultancy fees from Astra Zeneca, Astex, Clovis, GSK, GamaMabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, PharmaMar, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen and Takeda and serving as a shareholder of Gritstone.

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