

**LETTER TO THE EDITOR**

Children with cancer in the time of COVID-19: An 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy

To the Editor:

This report assesses the impact of the COVID-19 pandemic on pediatric cancer patients over an 8-week period elapsing from the day of the Italian outbreak (February 20, 2020) to the time of writing (April 15, 2020) in Lombardia region, the epicenter of the pandemic in Italy and one of the worst-hit areas in Europe. During the 8-week period, 155 467 confirmed COVID-19 diagnoses and 19 508 deaths due to the virus were reported in Italy, while Lombardia registered 63 098 positive cases (40% of all Italians affected) and 11 384 deaths.

Lombardia is the central region of northern Italy, covering an area of 23 863 km² with a population of 10 million (population density 421.6/km²). The region has six pediatric onco-hematology centers. Cancer incidence in the region's population aged 0-18 years is approximately 19/100 000, with 320 new cases expected to occur each year.¹ In addition, 40-50% additional patients come from other Italian regions (often from the south) or from abroad.

In the days following the outbreak, the pediatric oncology centers in the region were suddenly faced with an unexpected emergency situation exceeding the capacity of Lombardia's health system² and had to urgently adjust accordingly: they continued to develop oncological treatments, while implementing measures to minimize the risks of infections, to test for COVID-19 high-risk cases and to adequately manage COVID-19-positive patients,³ as reported in Table 1.

In all, in the study period, there were 347 accesses for inpatients registered by the six centers and 4138 for outpatients (total 4485). Most patients accessed a center multiple times during the 8-week period. Overall, 286 patients were tested for COVID-19, 212 of them asymptomatic (187 tested for screening purposes and 25 due to close contact with diagnosed cases) and 74 symptomatic (Table 2).

Twenty-one cases of COVID-19 infection were identified (48% of them males), with a median age of 6 years (range 1-17). In particular, six cases emerged from among the 187 patients screened, six among the 25 tested due to close contact with diagnosed cases, and nine among the 74 patients tested because they had flu-like symptoms. Tumor types of the 21 positive cases were as follows: 10 leukemias, five soft tissue or bone sarcomas, two lymphomas, two hepatoblastomas, one central nervous system tumor, and one colon carcinoma. Fifteen of these patients were on treatment, and six had completed their treatment and were in follow up. The patients' cancer treatments were modified in 10 cases (delaying chemotherapy or reducing drug doses, postponing surgery). Two patients experienced complications of the viral

TABLE 1 Measures implemented during the COVID-19 pandemic by the six pediatric onco-hematology centers in Lombardia^a

Restrictive measures to minimize the risks of in-hospital infections for patients and staff members

- 1) Containing the risk of spreading the infection by restricting access to the pediatric onco-hematology units; adopting strict hygiene measures for patients, parents, and staff; paying particular attention to hand washing; imposing the use of personal protective equipment (surgical masks) by staff, patients, and caregivers; allowing only one parent to assist patients; and refusing access to educators, teachers, and even volunteers to comply with the central government's legislation.
- 2) Rescheduling nonurgent hospital visits and relying on telephone consultations for follow up.
- 3) Specific and accurate triage on the day before appointments necessitating admission.
- 4) Identifying separate, protected clinical management paths for cancer patients and suspected cases of COVID-19.

Test for COVID-19

- a) Tests were based mainly on molecular testing on swabs.
- b) Chromatography was used for subsequent validation at one center.
- c) CT scans occasionally enabled suspected cases to be diagnosed, and molecular testing subsequently confirmed these cases.
- d) Asymptomatic patients and healthcare professionals were not routinely tested for COVID-19, in accordance with Lombardia Health Authority guidelines (this was partly due to a shortage of test kits).
- e) Testing was reserved for symptomatic suspected cases or their contacts.
- f) Screening tests were reserved for hematopoietic stem cell transplantation recipients prior to conditioning, for stem cell donors, and for candidates for surgery or invasive procedures such as endoscopy, and any procedures requiring general anesthesia.
- g) At specific pediatric centers, all patients accessing the facilities could be screened on admission for a limited time for research purposes.

Management of COVID-19-positive cancer patients

- 1) Patients with no coronavirus symptoms: The feasibility of postponing their chemotherapy was considered, either for 2 weeks or until two negative tests were obtained.
- 2) Patients who experienced symptoms were managed according to regional and institutional protocols.

^aThe six pediatric onco-hematology centers in Lombardia: Milano, Fondazione IRCCS Istituto Nazionale dei Tumori; Monza, MBBM Foundation/San Gerardo Hospital; Pavia, Fondazione IRCCS Policlinico San Matteo; Brescia, Spedali Civili; Bergamo, Papa Giovanni XXIII Hospital; Varese, Del Ponte Hospital. All the centers are affiliated to the Italian pediatric oncology cooperative group (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP]).

TABLE 2 Data collected regarding observed cases and patients tested for COVID-19 in the six pediatric onco-hematology centers in Lombardia over the first 8 weeks of the pandemic (February 20 to April 15, 2020)

| | Milano | Monza | Pavia | Brescia | Bergamo | Varese | Total |
|---------------------------------------------------------------------|-------------------|--------------------|-------------------|---------|---------|--------|--------|
| New cancer cases diagnosed yearly in the last 3 years | 230 | 90 | 60 | 45 | 40 | 20 | 485 |
| Between February 20 and April 15 | | | | | | | |
| New observed/expected ^a cancer diagnoses | 25/36 | 1/15 | 4/9 | 7/7 | 3/6 | 2/3 | 42/76 |
| Inpatient admissions | 112 | 70 | 69 | 49 | 33 | 14 | 347 |
| Outpatient accesses | 1133 ^b | 1462 ^c | 932 | 271 | 40 | 300 | 4138 |
| COVID-19-positive cases/asymptomatic patients screened | 2/10 | 2/101 ^d | 6/54 ^e | 0/26 | 2/21 | – | 12/212 |
| COVID-19-positive cases/patients tested due to symptoms or contacts | 4/6 | 2/8 ^f | 1/54 | – | 2/2 | 0/4 | 9/74 |
| Total COVID-19-positive patients | 6 | 4 | 7 | 0 | 4 | 0 | 21 |
| Patients with severe COVID-19-related complications | 1 | 1 | 0 | 0 | 0 | 0 | 2 |
| Patients whose cancer treatment was changed | 5 | 2 | 2 | 1 | 0 | 0 | 8 |

^aExpected newly diagnosed cases calculated from the mean for the same period in the previous 3 years.

^bPlus 861 phone consultations.

^cPlus 741 phone consultations.

^dNinety-nine rapid chromatography tests are included in this figure and were performed in consecutive patients for the purpose of a subsequent validation based on standardized serological tests.

^eMolecular tests for screening purposes were performed in a selected high-risk population, including leukemia and patients that had transplants.

^fOne case had two negative swabs but was positive in bronchoalveolar lavage (BAL).

disease, that is, one, with a diffuse intrinsic pontine glioma and existing neurological respiratory impairments, developed ab-ingestis pneumonia requiring inward respiratory support; another, with Hodgkin's lymphoma, who had previously been given radiotherapy, developed atypical bilateral pneumonia with mild symptoms.

As further finding, we registered a total of 42 newly diagnosed cancer patients <18 years old, representing 55% of the number expected. This might reflect a delayed access to healthcare services for logistics and parents' behavior (in an attempt to avoid the risk of COVID-19 infection), as well as a lack of patient referrals from other Italian regions or from abroad. Noteworthy, a decrease in new cases, exclusively involving B-lineage childhood acute lymphoblastic leukemia (ALL), was observed in 2003 in Hong Kong during the outbreak of severe acute respiratory syndrome (SARS). The drop in diagnostic rate was not followed by a subsequent rebound, and it was tentatively suggested that this was due to restrictions on movement meaning a lower exposure to common infections possibly involved in the B-ALL tumorigenesis, according to the multiple-hit theory.⁴

Compared with the dramatic situation observed in Lombardia's general population over the same period, our data confirm that relatively few pediatric cancer patients had clinical signs of COVID-19 or tested positive for the virus, and that severe COVID-19 related illness are rare. Though a longer observation period (patients may develop clinical complications later on) and larger cohorts would need to be investigated, it seems that the risks of infection related to their underlying disease and state of therapy-induced immunosuppression may be counterbalanced by the protective effect of young age.⁵⁻¹⁰

The policy adopted by the Lombardia healthcare system at the time of the virus's sudden, dramatic spread (eg, focusing tests only on symptomatic individuals) prevented any large-scale screening efforts, as well as a comparison between the incidence of COVID-19 infection

in our patients and in the region's general population, because our patients were tested much more often, enabling us to detect cases that would otherwise have gone undiagnosed.

Although preliminary, our findings suggest that anticancer treatments for pediatric patients can continue with no major adjustments. Since pediatric tumors are generally very aggressive and require intensive treatment, postponing or modifying these therapies may jeopardize their efficacy and reduce patient cure rates.

In the present scenario dominated by COVID-19, it is crucial that we provide patients and families with adequate support and information on measures to prevent the infection and associated risks. An adequate awareness is essential to avoid panic and inappropriate behavior, and to ensure prompt reporting of any suspicious symptoms of the viral infection, to facilitate early diagnosis and treatment modulation.¹¹

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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