ANTI-Varicella zoster vaccination in contacts of children receiving antineoplastic chemotherapy: a prospective pilot study

Vaccinazione anti-varicella nei contatti dei bambini sottoposti a chemioterapie: studio prospettico pilota

Anna Timitilli¹, Luisella Bertoluzzo¹, Concetta Micalizzi², Maura Faraci², Guia Hanau², Rossella Ricci³, Raffaella Giacchino¹, Elio Castagnola¹
¹Unit of Infectious Diseases; ²Unit of Haematology and Oncology; ³Laboratory of Clinical Chemical Analysis and Microbiology, G. Gaslini Children’s Hospital, Genoa, Italy

INTRODUCTION

Varicella is an acute, contagious disease with air-born transmission caused by varicella zoster virus (VZV), that may be severe in children receiving antineoplastic chemotherapy [1]. During aggressive phases of treatment social activities are missing and therefore hospital environment and the familiar nucleus become the most important sources for varicella [2]. The live-attenuated vaccine has been demonstrated effective both in normal and immunocompromised children, but in children with cancer its administration requires a temporary discontinuation of chemotherapy that could be detrimental for the final outcome of the underlying disease [3-10]. Moreover several cases of VZV infection by vaccinal strains have been reported during aggressive chemotherapy for acute lymphoblastic leukemia [11]. In 2000 the Infectious Diseases Section of the Italian Association of Pediatric Hematology and Oncology published a statement against anti-varicella vaccination in children with cancer, but suggested to vaccinate health care workers and patients’ household contacts [12]. We report the results of a pilot program of anti VZV vaccination in negative household contacts of children receiving antineoplastic chemotherapy.

METHODS

All new patients aged less than 18 years admitted at the Department of Pediatric Hematology and Oncology of “G. Gaslini” Children Hospital (GCH) in Genoa, Italy, for chemotherapy of a malignancy or for receiving hemopoietic stem cell transplant from April 2004 to April 2005 were eligible for this study. In this period an anti VZV vaccine was commercially available, but it was not still inserted in the Italian general vaccination program. Since GCH had activated a program of VZV screening and vaccination of all health care workers, the attention was focused on all other subjects with frequent contact with the patients (parents, brothers and sisters, grandparents, baby-sitters, cousins, etc.), from here forward defined as contacts. The possibility of a previous VZV infection of the patients or their contacts was assessed by means of clinical history [13]. In case of uncertainty a serologic test was offered. In patients the detection of antibodies should be performed before the first administration of blood products or immunoglobulins. Anti VZV IgG and IgM antibodies were determined by using enzyme immunoassay techniques and individuals with VZV antibodies concentrations below 1 UI were considered susceptible to the infection (i.e. “negative”) [14].
Anti VZV vaccination by means of Oka/Merck strain was offered to all the negative contacts of negative patients. After obtaining an informed consent, children aged 18 months to 12 years received a single 0.5 ml dose, while subjects older than 13 years received a 0.5 ml dose followed by a second 0.5 ml booster dose 4 to 8 weeks later.

The GCH Ethical Committee approved the study. Sanofi Pasteur MSD - Italy, provided for free all the needed doses, but did not interfere in any case with the program and the evaluation of its results.

**RESULTS**

During the study period 216 patients were admitted to GCH with a neoplastic disease, 7 (3%) were admitted only for counselling and 2 died because of their underlying disease before any evaluation. The remaining 207 patients, with a median age of 4.9 years (range 0-26.5), were eligible for the study, but in 49 (24%) of them no history of previous varicella was collected nor serological samples for detection of anti VZV antibodies were available before any transfusion. Poor clinical conditions of the patient (who cannot afford another blood sampling) (in 35 cases) and physicians forgetfulness (in 14 cases) were the causes indicated for this missing data. As a consequence, only 158 (76%) patients were really eligible for the study. Among them, 32 (20%) had a previous history of varicella or were already vaccinated against VZV. Antibody search was performed in the remaining 126 and 51 (40%) resulted negatives. These patients had 110 household contacts, with a median age of 34.7 (range 1.2-68.4), available for clinical and laboratory screening for varicella: 52 (47%) had a positive clinical history and other 44 (40%) with unclear clinical history were positive for anti VZV antibodies. Therefore, vaccination was offered to 13 (12%) of household contacts of VZV-negative children with cancer and was actually performed in 7. Among the 6 remaining cases, 3 were not vaccinated since younger than 15 months, and 3 because of parental refusal, in spite of previous agreement with the screening program. None of the vaccinated subjects developed adverse events related with the vaccination program. During the study period no case of varicella was reported in patients attending the day-care Center or normal ward of the Department of Hematology and Oncology, while 3 cases of herpes zoster were observed.

**DISCUSSION**

Varicella may represent a severe complication for children with cancer [1, 11, 15]. Vaccination may performed by means of a living, attenuated virus, but it cannot be administered to the most severely immunocompromised patients, that on the contrary are those at risk of the most severe disease [11, 15].

We prospectively evaluated the feasibility of a vaccination program in household contact of VZV negative children undergoing antineoplastic chemotherapy. The major difficulty we observed regarding this strategy was represented by physicians’ attitude. In fact, in 24% of patients physicians did not collect the history and/or did not perform an anti VZV antibody test before the patient’s first transfusion, and this reduced the patients accrual. This aspect underlines the need of better protocols and instructions for pediatric oncologists to ask for patients’ clinical history and to implement mandatory serologic testing before starting chemotherapy.

Anyway, we observed that 67% of Italian children undergoing antineoplastic chemotherapy had a positive history of varicella or anti VZV antibodies, as 87% of their household contacts, in a period when anti VZV vaccination was recommended but not included in routine vaccination programs. As a consequence, only a small group of household contacts of children with cancer (12%) was eligible for VZV vaccination and this low number does not allow any consideration about the efficacy of this strategy in reducing the incidence of varicella in children with malignancy. Nonetheless the vaccination was safe for the recipients and no secondary case in the immunocompromised contacts was observed. However, in near 1/4 of the eligible subjects, vaccination was refused, in spite of a previous complete agreement to the study program. In all cases people argued about a fear of possible risk related with the vaccine, not for the immunocompromised patient, but for the contact who should be vaccinated. The refusal of vaccine administration represents a well know problem that require a relevant, focused, well-organized communication between the parents and physicians, especially in the setting of a preventable disease for
children with severe immunocompromise and in presence of an effective, safe and well tolerated vaccine, at least for normal subjects [4, 16].

In conclusion, our pilot study demonstrates the difficulties in the implementation of an anti VZV-vaccination program directed towards household contacts of children receiving antineoplastic chemotherapy. At present, pediatric oncologists attitude, especially the feeling that the patient could not afford another blood sampling at time of diagnosis of the underlying disease, and parental refusal, for the fear of vaccine-related adverse events, represent the major challenges against the complete success of this strategy in countries where VZV vaccination is not inserted in the general vaccination program. This suggests the need of protocols for the evaluation of infectious complications in children with cancer shared between oncologist and infectious diseases specialists and the need of a good information of parents about the efficacy and safety of vaccines that could reduce this risk.

**Key words:** varicella-zoster, vaccination.

---

**SUMMARY**

Varicella may be a severe infection in children with malignancy. Varicella vaccination is either not recommended for immunocompromised children or it requires temporary discontinuation of immunosuppression. We prospectively evaluated the feasibility of a varicella vaccination programme of household contacts of varicella-negative children receiving antineoplastic chemotherapy. From April 2004 to April 2005, 207 children were evaluated; in 49 (24%) the attending physicians collected no history about previous varicella and performed no serological evaluation before any transfusion. Among the 158 patients with complete history and/or a screening test, 51 (32%) were negative, with a total of 110 household contacts eligible for the study. Of these, 13 (12%) subjects resulted negative for varicella. In three of them vaccination was not performed due to parental refusal. This study demonstrates the difficulties in implementing a varicella vaccination programme targeting negative household contacts of immunocompromised children. The attitude of paediatric oncologists and parental refusal currently represent the main challenges against the complete success of this strategy in countries where VZV vaccination is not inserted in the general vaccination programme.

---

**RIASSUNTO**

La varicella può rappresentare una grave complicanza in corso di chemioterapia per una neoplasia in età pediatrica. La vaccinazione contro il virus VZV non è raccomandata in corso di terapie antineoplastiche e non ne richiede la sospensione temporanea, con possibile riduzione dell’efficacia della chemioterapia sulla malattia di base (ridotta dose-intensity). Nel periodo compreso tra aprile 2004 e aprile 2005 è stata valutata prospetticamente la fattibilità di un programma di vaccinazione dei contatti familiari di bambini VZV-negativi sottoposti a chemioterapia antineoplastica o trapianto di midollo osseo presso il Dipartimento di Ematologia ed Oncologia dell’Istituto “G. Gaslini” di Genova.

Durante il periodo di osservazione, sono stati valutati 207 bambini, ma in 49 (24%) di essi il medico curante non aveva effettuato una anamnesi mirata ad identificare una precedente varicella né un prelievo per la determinazione degli anticorpi anti-VZV prima di iniziare un programma trasfusionale. Tra i 158 soggetti con anamnesi e/o sierologia completi, 51 (32%) sono risultati negativi, con un totale di 110 contatti familiari eleggibili per lo studio. In questo gruppo di soggetti, 13 (12%) risultavano negativi per storia clinica e/o anticorpi anti-VZV. In 3 di essi, tutti minori, la vaccinazione non è stata eseguita per rifiuto dei genitori.

Questo studio dimostra le difficoltà nell’organizzare un programma di vaccinazione anti-VZV nei contatti di bambini immunocompromessi. L’atteggiamento degli oncologi pediatri e il rifiuto dei genitori alla vaccinazione hanno rappresentato i principali ostacoli al successo di questa strategia, da attuare in assenza di una vaccinazione di massa contro VZV.
REFERENCES