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Immunity against vaccine-preventable potentially neurotropic diseases in children treated for malignant brain tumours with HIT-91 chemo- and radiotherapy

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Abstract

Following surgery, chemotherapy and/or irradiation, patients with malignant brain tumours are at risk of neurotropic diseases, although these are partly vaccine-preventable. In a retrospective, controlled, observational study, the impact of the German-Austrian chemo- and radiotherapy protocol (HIT-91) on antibody concentrations against vaccine-preventable diseases and on vaccination behaviour was analysed. A significant level of seronegativity for measles- and mumps-IgG, and a reduced protection induced by inactivated vaccines was observed after HIT-91 therapy. Failure of seroconversion following measles and mumps live vaccinations was assessed in the HIT-91-treated group and in a group with benign brain tumours (BBT). Analysis of cellular immunological parameters revealed significant aberrations in the HIT-91-treated group 36 months after completion of HIT-91 therapy. A retrospective analysis of the patient's vaccination history revealed an incorrect risk perception concerning the choice of vaccinations. We therefore recommend clinical vaccination with serosurveillance in patients who have undergone treatment for brain tumours.

Keywords: Brain tumour; HIT-91 therapy; Vaccine-preventable diseases; Neurotropic viruses; Vaccination; Waning immunity

1. Introduction

Overall survival of children with malignant brain tumours has improved over the last two decades [1] leading to an increase in the concern over treatment-related effects. Infiltrating tumour growth and surgical intervention may cause irreversible neurological deficits. In addition, radiation is associated with white matter destruction [2]. Prevention of any additional damage to the central nervous system (CNS) of these patients is therefore of paramount importance. We present strong arguments in favour of protection of paediatric patients with brain tumours, after successful treatment, against avoidable secondary lesions caused by vaccine-preventable infections. Measles virus may cause cerebral endothelial cell infection [3] which should particularly be avoided in patients who have the sequela of irradiation-induced endothelial damage. Taking into account that mortality rate from measles in the healthy population of developed countries is one in 1000 [4], the risk of fatality is above this average in patients following immunosuppressive therapy. Patients with brains that are operated upon, irradiated and treated with HIT-91 may be at an increased risk for a severe course of infections with neurotropic viruses. Up to 5 in 1000 cases of mumps encephalitis have been reported and there may be an even higher risk in brain tumour patients [5]. Although aseptic mumps meningitis is a benign condition, hospitalisation is required in former brain tumour patients, in order to exclude a relapse. In rare cases, rubella encephalitis may also need to be excluded.

Little attention has been given to vaccine-preventable neurotropic diseases in patients with brain tumours. Studies on humoral immunity in patients following treatment for leukaemia indicated persistent defects [6,7]. We report on the impact of the chemo- and radiotherapy protocol HIT-91 [8] on the seroprofiles of vaccination-preventable diseases and on vaccination policies.

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2. Patients and methods

2.1. Patients

Our study included 30 patients in complete remission from their malignant brain tumours following HIT-91-therapy, 61 patients with benign brain tumours (BBT-patients) after surgical interventions without the need for cytostatic therapy and 38 patients without tumours. We studied 12 female and 18 male patients with a mean age of 12.2±4.7 years (range 4–22 years). All laboratory tests and the patient's vaccination history were assessed 36 months (median 25 months, range 1–108 months) after completion of HIT-91 therapy. Histological types were 21 medulloblastoma, 5 ependymoma and 4 supratentorial primitive neuroectodermal tumours (PNET). The HIT-91 protocol consisted of craniospinal irradiation with 36 Grays and a boost to the tumour bed for a total dose of 54 Grays with either pre- ($n=11$) or post- ($n=17$) irradiation chemotherapy. Patients younger than 3 years ($n=2$) received front-line intravenous (i.v.) chemotherapy and intrathecal methotrexate, followed by craniospinal irradiation as outlined above.

Pre-irradiation chemotherapy consisted of ifosfamide 3 g/m^2/day and etoposide 150 mg/m^2/day (days 1–3), followed by two cycles methotrexate 5 g/m^2/day, and a third block with cisplatin 40 mg/m^2/day and cytarabine 400 mg/m^2/day (days 1–3). The three blocks were administered in 2 week intervals and repeated once. Post-irradiation chemotherapy consisted of 8 cycles lomustine 120 mg/m^2/day (day 1), cisplatin 70 mg/m^2/day (day 1) and vincristine 1.5 mg/m^2/day (days 1, 8, 15) every six weeks [8].

Patients with PNET received an additional cycle of etoposide 100 mg/m^2 and ifosfamide 1500 mg/m^2 (days 1–3) and cisplatin 20 mg/m^2 (days 1–2). Additional immunosuppressive medication (e.g. steroids) was not administered.

Sixty one BBT-patients (24 females and 37 males) were included with a mean age of 11.9±5.7 years (range 2–22 years) after resection of histologically-benign tumours.

The control group consisted of 17 female and 21 male patients with a mean age of 10.6±4.8 years (range 2–18 years) with a comparable vaccination history. Immunological disorders were ruled out by means of evaluation of a complete history focusing on infectious diseases and thorough assessment of cellular immunological parameters.

Informed written consent was obtained from the participants or their parents. The study was approved by the local ethical committee.

2.2. Methods

Determination of serum immunoglobulins (Ig) against vaccine-preventable diseases in fresh sera was part of the routine follow-up. Vaccination documents were evaluated focusing on neurotropic diseases (measles, mumps, rubella, varicella and tick-borne-encephalitis (TBE)) and on diphtheria and tetanus. Other vaccinations were not the subject of this study. None of the patients had received blood products 3 months prior to testing. Measles, mumps, rubella and varicella serum IgG and IgM antibodies were determined as part of the routine follow-up at the Institute of Virology, University of Vienna. The commercially available test kits used were obtained from Dade-Behring (Enzygnost Anti-measles virus IgG, Anti-mumps virus IgG and Anti-Varicella zoster virus (VZV)/IgG, with detection limits of 150 mIU/ml for measles and 50 mIU/ml for Anti-VZV, respectively), the rubella IgG enzyme-linked immunosorbant assay (ELISA) was obtained from Medac (Germany), detection limit <5 IU/ml. Positive and borderline IgG were considered to be protective in the long-term except for borderline measles IgG which were not considered protective in the long-term [9].

Diphtheria and tetanus antibodies were determined by ELISA tests at the Immunologic Outpatients Clinic, Vienna. For both, long-term protection was obtained at >0.1 IU/ml, partial protection was inferred if the values fell between 0.01–0.1 IU/ml [9].

TBE antibodies were determined by routine ELISA and were considered protective at >120 Vienna units (VU)/ml [10].

Lymphocyte numbers and subsets were evaluated by the afore-mentioned Immunologic Outpatients Clinic, a certified laboratory for the assessment of immunological routine parameters [11]. Certified routine diagnostic quantification of lymphocyte counts was performed by staining the cells with monoclonal antibodies against CD-3, CD-4, CD-8, CD-19 and CD-56 prior to analysis on a flow cytometer.

2.3. Statistics

Unilateral Pearson Chi Square tests ($\alpha=0.05$) were performed. Quantitative results (TBE-, diphtheria-, tetanus-antibody concentrations and cell counts) were analysed using the Kruskal–Wallis test ($\alpha=0.05$).

3. Results

In general, HIT-91 patients had a significantly higher percentage of seronegatives for measles, mumps and rubella antibodies compared with patients who had not received cytostatic therapy. Fig. 1 gives an overview of the immunity observed in the three study groups. Details of the seronegatives that were observed despite vaccination are shown in Figs. 2–4.

3.1. Measles

We found a significant reduction in the frequency of protective measles IgG antibodies in the HIT-91 group: IgG were negative in 21/29 (72%) HIT-91 patients, in 22/61 (36%) BBT-patients and in 17/37 (46%) healthy controls ($P = 0.0025$) (Fig. 1). Fourteen (67%) of the seronegative HIT-91 patients had one measles vaccination and one patient had 2 doses before the onset of HIT-91, three of them were vaccinated once again and two of them twice after HIT-91. 4 (19%) of the seronegatives were not vaccinated, and in 2 patients (10%) the documentation was missing (Fig. 2). Ten (45%) and 6 (27%) of the seronegative BBT-patients had 1 and 2 measles vaccinations, respectively. One (5%) of the seronegative BBT-patients was not vaccinated, and in 5 the documentation of vaccination was missing. Four (24%) and 5 (29%) of the seronegative controls had 1 and 2 measles vaccinations, respectively. One (6%) of the seronegative controls was vaccinated three times, one of the seronegatives (6%) was not vaccinated. In 6 controls, the documentation of vaccination was missing.

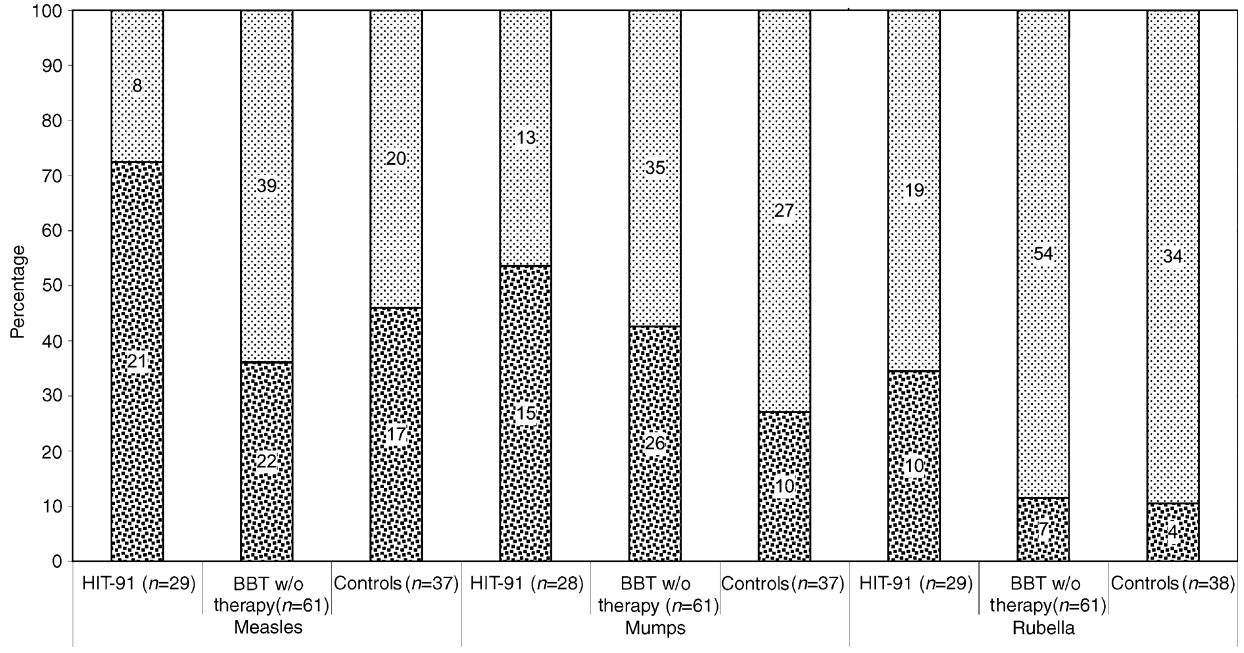

Fig. 1. Seropositivity and -negativity of measles, mumps and rubella IgG in HIT-91 patients, BBT-patients and controls. Seronegatives: dense dots, seropositives: light dots. w/o, without.

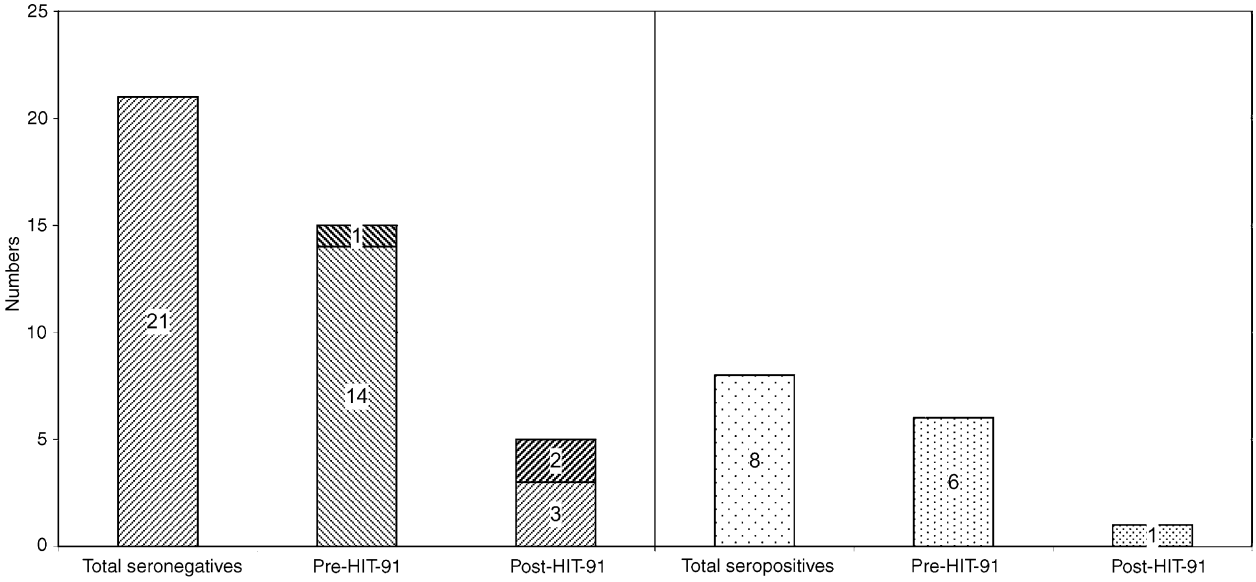

Fig. 2. Measles vaccination status in seronegative and seropositive HIT-91 patients. Patients vaccinated before (Pre-HIT-91) and additionally after HIT-91 (Post-HIT-91). Seronegatives striped bars; dark stripes: two vaccinations. Seropositive dotted lines.

3.2. Mumps

A significant lack of mumps IgG antibodies was found in the HIT-91-group: IgGs were negative in 15/28 (54%) HIT-91 patients, in 26/61 (43%) BBT-patients and in 10/37 (27%) controls ($P = 0.043$) (Fig. 1).

Eleven (73%) of the seronegative HIT-91 patients had a mumps vaccination once pre- HIT-91 therapy, two of them were vaccinated once again after HIT-91 treatment. Four (27%) of the seronegatives were not vaccinated (Fig. 3). Eleven (42%) and 6 (23%) of the seronegative BBT-patients had one and two mumps vaccinations, respectively. Two (8%) of the seronegative BBT-patients were not vaccinated, and in 7, the documentation was not available. Two (20%) and 1 (10%) of the seronegative controls had one and two mumps vaccinations,

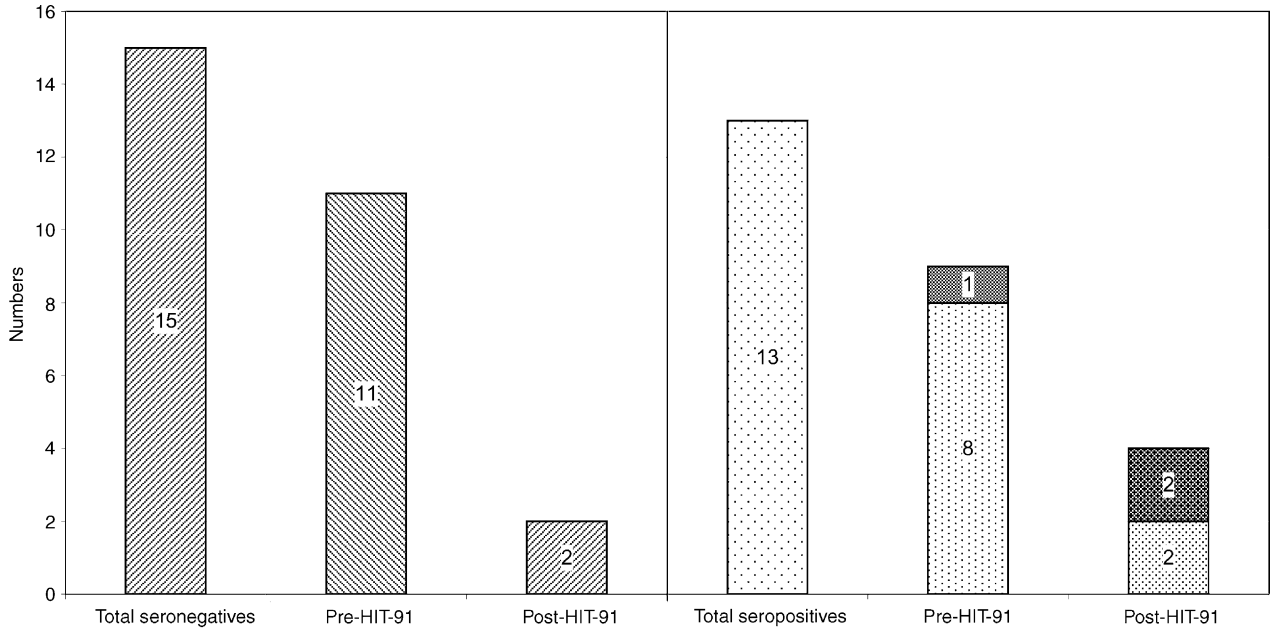

Fig. 3. Mumps vaccination status in seronegative and seropositive HIT-91 patients. Patients vaccinated before (Pre-HIT-91) and additionally after Hit-91 (Post-HIT-91). Seronegatives striped bars. Seropositives dotted bars; dense dots: two vaccinations.

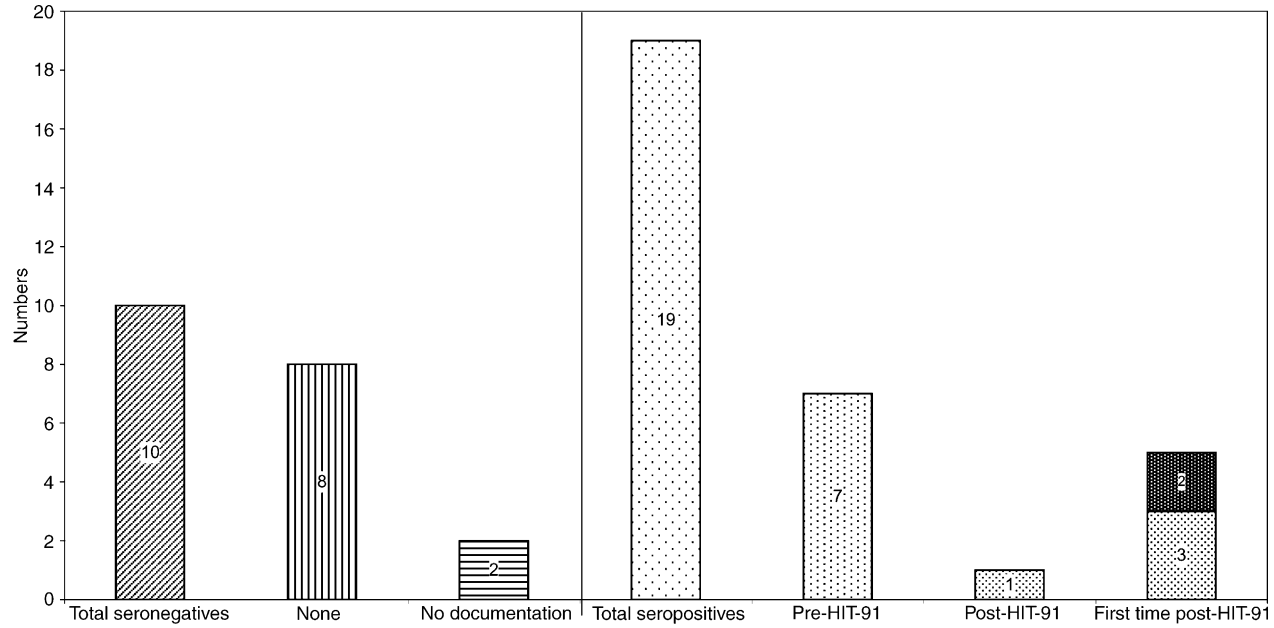

Fig. 4. Rubella vaccination status in seronegative and seropositive HIT-91 patients. Patient vaccinated before (Pre-HIT-91) and additionally after HIT-91 (Post-HIT-91). Seronegatives striped bars. Seropositives dotted bars; dense dots: two vaccinations.

respectively. In 8 controls, the documentation was not available.

3.3. Rubella

Rubella-specific IgG antibodies were negative in 10/29 HIT-91 patients (34%), in 7/61 BBT-patients (11%) and in 4/38 healthy controls (11%) ($P=0.055$) (Fig. 1).

Eight (80%) of the seronegative HIT-91 patients had no rubella vaccination, 2 patients lacked documentation (Fig. 4). One (14%) of the seronegative BBT-group was vaccinated against rubella once. Four (57%) of the seronegative BBT-patients and 1 (25%) of the seronegative controls were not vaccinated. In 2 BBT-patients and 3 controls, the documentation was missing.

3.4. Varicella zoster (VC)

VCV-IgG antibodies were negative in 7/26 (27%) HIT-91 patients, in 12/61 (20%) BBT-patients and in 11/37 (30%) healthy controls ($P=0.248$). None of the patients in any of the groups were vaccinated for VCV.

3.5. Diphtheria

Diphtheria-IgG antibodies below the long-term protective value 0.1 IU/ml were found in 10/30 (33%) HIT-91 patients, in 16/56 (29%) BBT-patients and in 6/34 (18%) healthy controls ($P=0.167$) (Fig. 5).

Nine (90%) of the long-term unprotected HIT-91 patients were vaccinated for diphtheria (range 3–5 single doses, one patient was given only one dose); one patient had no documentation. Fourteen (88%) of the long-term unprotected BBT-patients were vaccinated for diphtheria, in 2 patients, the documentation was absent. Two (33%) of the controls were vaccinated for diphtheria. In 4 controls the documentation was not available. A significant quantitative reduction in the diphtheria IgG level was found in the HIT-91-group with a mean of 0.26 ± 0.29 IU/ml (range 0.01–1) compared with the BBT-patients 0.57 ± 0.87 IU/ml (range 0.01–4.89), and controls 0.68 ± 0.82 IU/ml (range 0.06–3.73) ($P=0.013$).

3.6. Tetanus

A significant number of HIT-91 patients had a tetanus-IgG level that was below the long-term protective value of 0.1 IU/ml. Antibodies below 0.1 IU/ml were found in 5/30 (17%) HIT-91 patients, in 1/56 (2%) BBT-patients and in 1/34 (3%) controls ($P=0.007$) (Fig. 5).

Combined diphtheria and tetanus vaccination was documented in 4 unprotected (80%) HIT-91 patients (range 3–5 single doses, 1 patient was given only 1 dose); in one patient no documentation was available. Both long-term unprotected patients in the control groups were vaccinated against tetanus. No significant quantitative

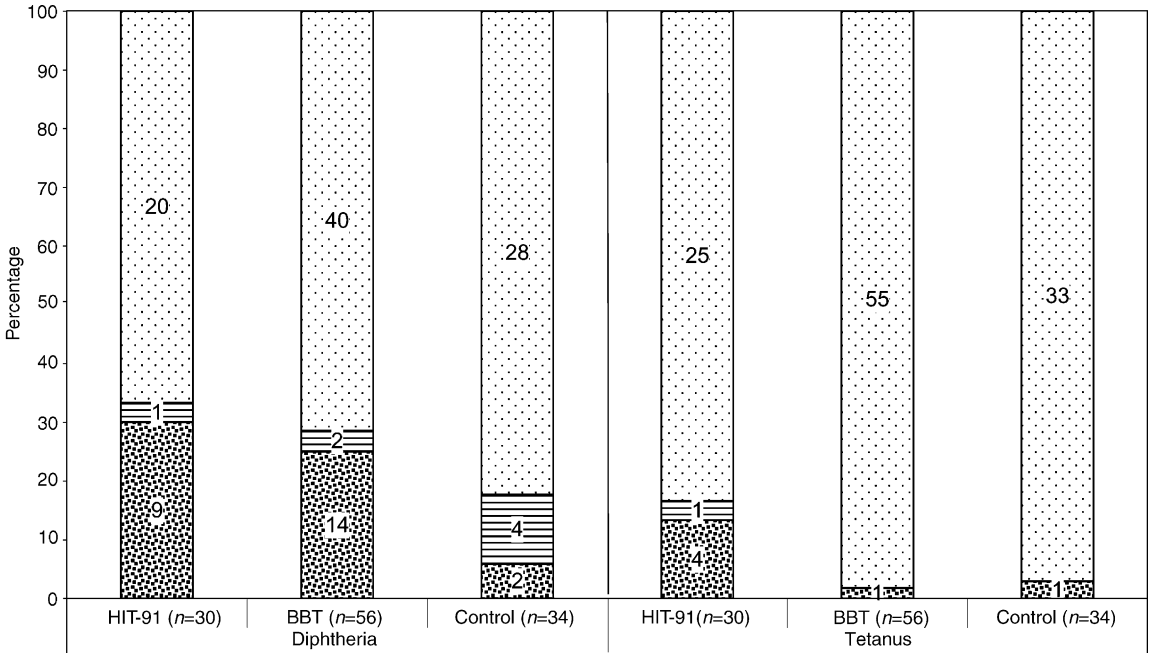

Fig. 5. Diphtheria and tetanus protection and vaccination status in HIT-91 patients, in BBT-patients and in controls. Long-term protection: light dots. No protection and unknown vaccination status; stripes. No protection despite vaccination: dense dots.

Table 1
Cellular counts in patients after HIT-91 therapy, in patients with benign brain tumours and controls. Bilateral Kruskal-Wallis test, the significance level was 0.05

	Leucocytes 10^9/l	Lymphocytes 10^9/l	CD-3 10^9/l	CD-4 10^9/l	CD-8 10^9/l	CD-19 10^9/l	CD-56 10^9/l
HIT-91 ($n=28$)							
Mean	4.860	1.633	1.033	0.521	0.559	0.307	0.217
Standard deviation	1.410	0.678	0.492	0.256	0.252	0.180	0.124
Range	2.400–8.700	0.264–2.950	0.100–1.809	0.055–0.916	0.090–1.118	0.048–0.974	0.071–0.546
Benign brain tumour ($n=56$)							
Mean	6.250	2.548	1.657	0.931	0.735	0.384	0.284
Standard deviation	2.080	1.184	0.518	0.330	0.224	0.210	0.159
Range	2.000–12.700	0.824–9.360	0.543–2.976	0.227–1.835	0.253–1.338	0.032–1.339	0.075–0.892
Control ($n=33$)							
Mean	6.820	2.883	1.847	1.007	0.870	0.424	0.318
Standard deviation	2.380	1.419	0.894	0.392	0.465	0.306	0.162
Range	3.700–15.200	0.970–7.440	0.446–5.292	0.223–2.103	0.253–2.714	0.082–1.400	0.029–0.797
P value	0.001	0.001	0.001	0.001	0.004	0.188	0.017

difference was found in the tetanus-IgG level: the HIT-91-group had a mean of 2.63±6.58 IU/ml (range 0.02–36.5), BBT-patients had a mean of 3.32±4.8 IU/ml (range 0.06–25), and the healthy controls had a mean of 2.66±2.9 IU/ml (range 0.07–13.1) ($P=0.071$).

3.7. TBE

TBE-IgG levels below the protective value of 120 VU/ml were found in 6/29 (21%) HIT-91 patients, in 3/56 (5%) BBT-patients and in 3/34 (9%) of the healthy controls ($P=0.04$). Four (67%) of the unprotected HIT-91 patients had not been vaccinated. One patient (17%) had received only two vaccinations prior to HIT-91 therapy and one patient had no documentation. Two (67%) of the unprotected BBT-patients had been vaccinated. In one patient, the documentation was missing, as was the case for the three unprotected controls.

A significantly lower TBE-IgG level was observed in HIT-91-group with a mean of 1497±1562 VU/ml (25-5605) compared with 3224±3723 VU/ml (12-20517) in the BBT-group and 3122±3824 VU/ml (4-14318) in the controls ($P=0.011$).

3.8. Leucocyte and lymphocyte counts

Total leucocyte and lymphocyte cell counts and CD-3, CD-4, CD-8, CD-56 subset counts were significantly reduced in the HIT-91-group compared with both control groups (Table 1). The numbers of CD-19-positive B cells appeared to be unaffected.

3.9. Antibody evaluation and vaccination history

Antibodies against vaccine-preventable diseases were (retrospectively) in 16 patients evaluated 30–108 months after HIT-91 and the data compared with the patient's vaccination history. Two of the 16 patients had not been vaccinated 27 and 58 months after completion of HIT-91 therapy. Eleven patients were vaccinated against TBE 5–35 months after HIT-91. Nine patients were vaccinated against poliomyelitis (OPV) 1–86 months after HIT-91. Seven patients were vaccinated with a combined diphtheria and tetanus vaccine 11–71 months after HIT-91. Six patients received the MMR vaccination 6–39 months after HIT-91. Four patients were vaccinated against hepatitis B 17–76 months after completion of therapy. Only one patient was vaccinated once against influenza 98 months after completion of therapy.

In the remaining 14 patients, antibodies against vaccine-preventable diseases were assessed 1–23 months after HIT-91-therapy, and an individually-tailored vaccination protocol was initiated.

4. Discussion

Paediatric brain tumours are the largest group of solid tumours and the leading cause of cancer-related morbidity and mortality in childhood [12]. Due to improved therapy protocols overall survival rates of patients with brain tumours are increasing, as is the significance of patients' quality of life. To our knowledge, no reports concerning immunological data with regard to vaccine-preventable diseases in patients with brain tumours have been published. The potential neurotropism of endemic viruses, like measles, mumps, rubella, varicella, influenza and TBE, may mean that patients who have undergone surgery, been irradiated and/or cytostatically-treated have a higher risk of severe complications. Due to the MMR vaccination, the incidence of such

infections has been reduced, but epidemics still occur in Europe [13]. Moreover, varicella vaccination is not implemented in European public health vaccination programmes.

In this study, we investigated patients' antibody concentrations against vaccine-preventable diseases in a group of subjects with malignant brain tumours treated with HIT-91 and compared these levels with those in healthy controls and a group with benign brain tumours.

The significant lack of measles IgG levels in 21 of 29 (72%) patients of the HIT-91-group strongly argues for a higher susceptibility to measles infection. In addition, 22 of the 61 BBT-patients (36%) were susceptible. Furthermore, 46% of the control group lacked protective measles IgG. In contrast to the documented immunisation rate of approximately 60–70% in seronegative subjects, the protection rate is unexpectedly low in all of the groups we studied. Since we regarded subjects with borderline measles serum IgG as susceptible, the control group also exhibited a high susceptibility. Indeed, the high rate of susceptibility is, in part, possibly due to these borderline results. Handling issues with regard to the vaccine may also partly explain the high susceptibility. However, our rates of susceptibility in both control groups were higher than the 20% found in the literature, using the same vaccine as in our study [14].

The healthy group may be protected by cellular immune responses [15], whereas patients after brain tumour therapy may have altered cellular immunological functions. This argument is underlined by our observation of a highly significant reduction in lymphocyte counts 36 months after cessation of HIT-91 therapy representing a late effect of craniospinal irridiation from the HIT-91 therapy leading to a reduced bone marrow reserve. Low CD-4 helper cell counts might contribute to a low response to vaccination after HIT-91 therapy and this might be observed long-term. This underlines the importance of individually-tailored vaccination schedules, taking into account a low number of lymphocytes as a potential contraindication for life virus vaccination. Individual vaccination could be based on vaccination history, on the level of serum antibodies and on cellular immunology data (CD-4/CD-8); the epidemiological situation should also be considered. Since the cell counts after completion of HIT-91 therapy are highly variable, we think that MMR vaccination after a fixed time (i.e. 6 months after completion of chemotherapy as recommended in the UK [16]) may not be appropriate in some of our HIT-91-treated patients.

Prolonged depressed immune responses during and after wild-type measles virus infection [17] deserve special attention in patients after cytostatic therapy. Moreover, in non-human primate models for measles virus infection, bone marrow was shown to be infected containing high titres of measles virus [18]. This led to the speculation that the growth and differentiation of progenitor cells are affected [19], which may be critical in patients even a long time after HIT-91-induced bone marrow depletion. Prolonged immunosuppression after measles infection may result in life-threatening pulmonary complications and opportunistic infections in post-treatment tumour-patients. It is also known that an attenuated measles vaccine may reduce T-cell immunity [15,20], but this effect does not last as long as that following wild-type infection [21]. Austria and some neighbouring countries are still endemic for measles due to the lack of herd immunity and this increases the risk of infection for brain tumour patients in these areas. Furthermore, the cut-off values for long-term protection are defined for healthy population with respect to usual exposure circumstances following an average challenge of the immunocompetent host [9].

The significant lack of measles antibodies in brain tumour patients after HIT-91 therapy, despite measles vaccination is similar to the results obtained in a study in 13 children two years after chemotherapy for acute lymphobastic leukaemia (ALL) [7]. Currently available measles vaccines induce seroconversion in more than 90% of children. Studies on the duration of vaccine-induced immunity suggest that waning immunity is uncommon in the healthy population [22], but may occur in special cohorts, such as in patients after cytostatic therapy. The impact of cancer and its therapy on the function of the humoral immune system and antibody production was reported in paediatric patients with various malignancies [23]. In 39 children treated for acute leukaemia, seropositivity for measles, mumps and rubella IgG declined by 13–21% after different chemotherapy protocols [6]. The major concern of neurotropic virus susceptibility in patients with brain tumours is the predictability of measles outbreaks [24] and the 200 times elevated risk of measles encephalitis in immunocompromised patients with a high fatality rate of up to 70% [25].

Regarding the significant lack of mumps IgG levels in the HIT-91 group, it is of note that, similar to measles, seronegativity occurred despite documented immunisation in 11 of 15 patients (73%). In the BBT-group, 65% of the seronegatives were vaccinated compared with only 20% of the seronegative controls. Despite the moderate contagiousness of mumps virus, infection is of concern in brain tumour patients, since up to 10% of patients infected with mumps can suffer from aseptic meningitis and sometimes encephalitis. Morbidity also includes epididymo-orchitis, oophoritis and deafness [26]. These complications should clearly be avoided in patients treated with gonadotoxic and ototoxic cytostatic agents, in order to avoid potentially additive effects.

Rubella was a leading cause of encephalitis in the pre-vaccination era, wherevas nowadays it is a rare condition [27]. In this study, only one patient did not

seroconvert after rubella vaccination supporting the facts that seroconversion rates in response to rubella RA 27/3 vaccination are close to 100% [28], and that antibodies are maintained long-term [29]. We assume that the HIT-91 therapy and/or brain tumour did not affect the outcome of rubella vaccination in our study. Rubella vaccine may be more immunogenic compared with the measles vaccine in our patients, but this cannot fully explain the different protection rates observed.

No differences in varicella seroconversion rates were found in the three groups. A general varicella vaccination programme has not yet been implemented in Europe. However, the neuroinvasiveness of varicella virus observed in a few cases has led us to strongly recommend vaccination in varicella-seronegative patients after brain tumour therapy.

In summary, the HIT-91-treated group had the best protection rates against the least neurotropic rubella virus, but had the worst protection rates against the most neurotropic measles virus.

In the HIT-91- and the BBT-group, 33% and 29%, respectively, were not protected against diphtheria in the long-term (<0.1 IE/ml). A high proportion of these patients were completely immunised in both tumour groups (80% and 88%, respectively). The significant quantitative reduction of diphtheria antibody concentrations in the HIT-91 patients compared with both control groups may be attributed to the HIT-91 therapy. A significant proportion of 17% in the HIT-91 group was not protected against tetanus (<0.1 IE/ml) in the long term. However, tetanus antibody concentrations did not differ significantly between the three study groups. Again 60% of the long-term unprotected subjects in the HIT-91-group and each of the long-term unprotected subjects in the control groups had been completely immunised.

The significant reduction of long-term protective TBE-IgG levels in HIT-91 patients is mainly due to insufficient vaccination (67%). However, BBT-patients also had a vaccination rate of 66%. Quantitative analysis of TBE-IgG revealed a significant low IgG level (mean 1497 VU/ml) in HIT-91 patients compared to the BBT and control group (mean 3324 VU/ml and 3122 VU/ml respectively), however, the TBE IgG was far above the protection limit of 120 VU/ml reflecting the high immunogenicity of the TBE vaccine.

Our results therefore argue for inconsistent seroconversion rates for measles and mumps despite vaccination; documented vaccinations did not ensure appropriate seroconversion. We recommend the determination of antibody concentrations of vaccine-preventable diseases before the onset of any cytostatic therapy. The successful treatment of malignancies has to include strategies for the prevention of infections. A major improvement of outcomes in the treatment of ALL was the prevention of non-bacterial infections (*pneumocystis carinii* and measles) [30]. ''Herd immunity'' to measles is crucial to avoid deaths, because no effective treatment for interstitial measles pneumonitis in the immunosuppressed is currently available [31,32] and the diagnosis of measles encephalitis in immunosuppressed patients is difficult [33].

Free access to public health immunisation programmes is offered. Nevertheless, 2 of 16 patients treated for malignant brain tumours skipped this programme and did not receive any vaccinations 27 and 58 months after HIT-91 chemo- and radiotherapy, although normal lymphocyte counts were documented in these patients. In HIT-91 patients who did receive vaccinations, an incorrect risk perception is observed with regard to the choice of vaccination with the TBE vaccine being favoured over the measles vaccine: only 6 of 16 HIT-91 patients received the MMR vaccination, in contrast to the 11 who received the TBE vaccination; TBE has a comparatively low morbidity in children. According to the antibody levels of the patients, the risk for encephalitis was highest in cases of measles virus infection, low in cases of mumps and remote in cases of rubella. However, due to intensive marketing activities, acceptance of the TBE vaccination was high, despite the fact that in children the risk of TBE-encephalitis after a tick bite is even more remote than rubella-encephalitis.

Our data highlight the need for individually-tailored, clinical-centred vaccination programmes including serosurveillance of patients after treatment for brain tumours.

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