New therapies

Interferon-alpha in childhood haematological malignancies

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Summary

The application of cytostatics has brought about a breakthrough in the treatment of childhood haematological malignancies in the past 20 years. Chemotherapy appears to be least successful in the rare, low and very high mitotic index diseases, which often have an enormous tumour-burden. The suitability of chemotherapy in minimal residual leukaemia is also of some doubt. In these situations a 'conservative' treatment may be more appropriate. Because interferon-alpha has a distinct mechanism of action, and a broad-spectrum haematopoietic inhibitory activity, it is relatively nontoxic and noncancerogenic, and it may have a role in the treatment of malignant haematological disorders, either as a mono- or combination therapy.

The exact indications and dosages for interferon in childhood malignancies are far from clear. Up to now, it has proved to be most efficacious in small tumour masses, providing a theoretical basis for application in minimal residual disease. Controlled clinical data, however, are not yet available. It remains to be determined whether or not interferon can be added to current chemotherapy protocols without a significant reduction of dose. Hopefully, a deeper understanding of the activities of interferon will allow us to plan better trials with combination treatments.

Keywords: interferon, childhood, haematological malignancies

The appearance of recombinant interferons has given a new 'impulse' to the field of clinical interferon research, as they removed the fear of virus transmission. Biochemically pure products have allowed dose-effect investigations to be carried out and permitted the use of different interferons for specific therapy.

Nevertheless, at present, few data are available on the paediatric use of interferons such as dosage (single dose, frequency), possible combinations, tolerance and late side-effects. The disorders in which interferon therapy is applicable are rare in childhood¹ (chronic B and C viral hepatitis, life-threatening haemangiomas, chronic idiopathic thrombocytopenic purpura, recurrent respiratory papillomatosis, and, in some cases, acquired immune deficiency syndrome, in addition to malignant haematological diseases). In this review the results of interferon-alpha therapy in childhood haematological malignancies to date are summarised.

The mechanism of interferon action

The interferons have antiproliferative, differentiation-inducing and immunomodulatory activities. The exact mechanism of action is not clearly understood. After binding to a specific high-affinity cell-surface receptor, rapid tyrosine phosphorylation of pre-formed protein subunits in the cytoplasm leads to formation of a heterotetramer which is bound to partially identified genes, so-called 'interferon-stimulated response elements'.² The genes which have been identified up to now as significant with respect to haematological impact (differentiation) are located in a cluster on the long arm of chromosome 1.^{3,4}

In some malignancies interferons function as tumour suppressors. In acute lymphoblastic leukaemia patients, homozygous or heterozygous deletions have been found (overall 29%) in the sequences of interferon-alpha and beta-1 genes.⁵ These alterations may play a role in both carcinogenesis and therapeutic susceptibility.⁶ In Langerhans cell histiocytosis interferon-alpha is used as an immune-restoring agent (increasing T suppressor and natural killer cell activity).⁷ The use of interferon to induce a graft-versus-leukaemia reaction after bone marrow transplantation is another area of intense study.

Chronic myeloid leukaemia

Two forms of chronic myeloid leukaemia exist in childhood. The first is the Ph chromosome-positive adult type, which is analogous to the disease of adulthood, the second is the Ph chromosome negative, so-called juvenile type.

The adult type is a disease of pluripotent stem cells, which takes a mean of 35 months until acceleration occurs.⁸ The only curative therapy currently available is allogeneic bone marrow transplantation. In adulthood the exact indications for interferon therapy have been established and its application is widespread.^{9,10} Between 30% and 44% of cases display a complete or near-complete disappearance of the Ph chromosome,^{10,11} and the haematological remission rate is about 75%. The results of interferon therapy are better than those of chemotherapy and it improves average survival.^{11,12} The best results are achieved when therapy is started in the first year.¹⁰

Some reports are available on interferon therapy of adult-type childhood chronic myeloid leukaemia. Dow applied interferon after a median of seven months cytostatic therapy (hydroxyurea, busulphan). In a group of 15 patients, haematological remission was achieved in 10 and cytogenetic conversion in four patients. At least 48 weeks of treatment were necessary. The mean survival was 51 months.¹³ Favre (cited in ¹) reported on the treatment of 25 patients. He achieved haematological remission in 17 cases; this was complete in five patients while partial cytogenetic conversions were achieved in six. The five-year overall projected survival was 80%.

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Indications of interferon-α in childhood haematological malignancies
<i>Absolute indication</i> (if no donor available) <ul style="list-style-type: none">• adult-type chronic myeloid leukaemia
<i>Relative indications</i> <ul style="list-style-type: none">• juvenile type chronic myeloid leukaemia• chronic myeloproliferative disorders other than chronic myeloid leukaemia (essential thrombocytosis, polycythaemia vera, myelofibrosis)• relapsing acute lymphoblastic leukaemia or non-Hodgkin's lymphoma (mainly of T-cell)• after bone marrow transplantation (autologous and allogeneic)• Langerhans cell histiocytosis

Box 1

Interferon: treatment regimes
<ul style="list-style-type: none">• adult-type chronic myeloid leukaemia: 5 MU/m² daily• juvenile-type chronic myeloid leukaemia: 200 000 IU/kg three times a week (± hydroxyurea)• relapsing acute lymphoblastic leukaemia or non-Hodgkin's lymphoma: 20–50 MU/m² daily according to tolerance for 10 days before and during chemotherapy• after bone marrow transplantation: 100 000 IU/kg every three days or 1 MU/m² daily after transplant• Langerhans cell histiocytosis: 2–3 MU/m² daily ± steroid

Box 2

The present authors applied interferon after three and a half years mitobronnitol therapy in one patient. A striking haematological effect was not observed at a dose of 5 MU/m²/day, (corresponding to the adult dose). In general, the results are similar to those in adulthood, although the impact on survival is still questionable. Probably, combined treatment (cytostatics plus interferon) will increase in the future because the results in adults are promising.¹⁴

Juvenile chronic myeloid leukaemia is characterised by granulocyte-macrophage colony-stimulating factor-independent growth of monocyte colonies *in vitro*.¹⁵ The disease is a myeloproliferative disorder of infancy which is insensitive to chemotherapy. The mean survival is less than 10 months.¹⁶ The only curative therapy is allogeneic bone marrow transplantation. On the basis of the interferon susceptibility of spontaneous colonies,¹⁸ several attempts have been made to apply interferon in this disease. The results, however, are controversial. In some patients interferon therapy has been unsuccessful.¹⁹ Mutz²⁰ observed a transitory improvement in one patient. Only one out of three patients showed a transient response in Elias' series.²¹ Baruchel¹ reported survivals of three and more than five years in two patients with monosomy 7. After failure of chemotherapy, Arico observed a long-lasting complete remission with interferon in one patient.²² Pechumer²³ and Suttorp²⁴ used interferon plus hydroxyurea successfully in one patient for six months and in another for three years until bone marrow transplantation. Omitting any of these medicines resulted in an increase of the leukocyte count. The usual interferon dose was 200 000 IU/kg three times a week.

Other chronic myeloproliferative disorders

Chronic myeloproliferative disorders other than chronic myeloid leukaemia (essential thrombocytosis, polycythaemia vera, and myelofibrosis) are very rare in childhood. In all of these interferon may represent a therapeutic alternative in adulthood.^{25–27} There have been no reports on the paediatric uses of interferon therapy in these disorders.

The present authors used interferon-alpha treatment in an 11-year-old patient with polycythaemia vera in a dose of 2 MU/m² twice a week. Phlebotomy, which had previously been required on a monthly basis, was not necessary during the first three months; the patients' complaints stopped immediately, she achieved a complete haematological remission, and her splenomegaly almost disappeared.²⁸

Acute lymphoblastic leukaemia and non-Hodgkin's lymphoma in relapse

Despite good results in the treatment of paediatric lymphoblastic diseases, one can hardly hope to cure relapsing cases with chemotherapy. As HLA-compatible bone marrow donors are often not available, the appropriate management of these patients is difficult. Interferon monotherapy has proved to be successful in lymphoproliferative diseases with a low proliferative rate in adulthood.^{29–32} In highly malignant lymphomas, it was combined therapy which extended the event-free survival.³³ Interferon was used simultaneously in relapsing acute lymphoblastic leukaemia and non-Hodgkin's lymphoma in childhood. In her initial study, Ochs reported promising results with 17 chemotherapy-resistant acute lymphoblastic leukaemia and non-Hodgkin's lymphoma children.³⁴ A complete remission of 11 months was achieved in one patient with T-cell acute lymphoblastic leukaemia, while in another, a brief disease stabilisation was observed.

In another study, Ochs tested the tolerability and therapeutic efficacy of high-dose interferon administered before and together with chemotherapy in 31 patients in first relapse.³⁵ Up to the start of chemotherapy (10th day) two patients had achieved partial remission. The interferon administered during chemotherapy did not influence the feasibility of the treatment. There was no significant increase (74%) in the complete remission rate.

In another study, Lauer³⁶ reported the results of interferon therapy of 20 T-cell lymphoid malignancies in chemotherapy-resistant relapse (two weeks induction therapy (10 doses) and then maintenance). One patient achieved complete and three others partial remissions. The median time of remission was however, short (27 days). Doses were very high in all three studies (20–50 MU/m² per dose).

The present authors have observed the transition of cutaneous T-cell lymphoma to leukaemia in one case.³⁷ After two years complete remission, a local (skin) recurrence was removed, since when the patient has received 2 MU/

m² interferon every three days. The efficacy cannot be assessed yet due to the short length of treatment (two months).

Based on synergism between interferon and chemotherapy, the Pediatric Oncology Group is starting phase II studies on relapsing T-cell acute lymphoblastic leukaemia and non-Hodgkin's lymphoma.

Bone marrow transplantation

The greatest problem associated with bone marrow transplants in malignant haematological diseases is relapse, particularly after autologous or T-cell-depleted grafting, due to the lack of graft-versus-leukaemia reaction. Increasing the intensity of conditioning does not result in a higher survival, in spite of a better elimination of the leukaemic cells, due to unacceptable toxicity. A possible therapeutic alternative is to use interferon in the posttransplant period, to enhance the graft-versus-leukaemia reaction (due to increasing HLA and minor non-HLA antigen expression and natural killer cell activity) and for its direct antitumour properties (the majority of results presented here are from adults). Meyers³⁸ treated 39 acute lymphoblastic leukaemia patients after transplant with 100 000 U/kg interferon-alpha every three days in a randomised fashion to prevent cytomegalovirus infection. The interferon had no impact on viral infection but there was a significantly lower relapse rate in the interferon group (36 *vs* 74%).

Klingemann investigated the tolerance of interferon after bone marrow transplantation in high-risk leukaemias in a phase I study. The maximum tolerated dose was 1 MU/m².³⁹ Nine out of 14 patients (60%) had a two-year event-free survival which compares favourably with data from the same institution in a group of patients with the same diagnosis not treated with interferon (21%).

Ratanatharathorn⁴⁰ reported the effects of cyclosporin A plus interferon administered after an autologous rescue in lymphomas and leukaemias. Interferon induced a spontaneously resolving graft-versus-leukaemia-like reaction confined to the skin in every case (13 patients). The effect of interferon seemed to be more important than that of cyclosporin A. The clinical relevance of this phenomenon is yet unknown.

Langerhans cell histiocytosis

This rare disease is characterised by clonal proliferation⁴¹ of cells resembling Langerhans cells of the epidermis. In cases of early presentation and organ dysfunction, prognosis is often unfavourable, despite aggressive chemotherapy.⁴² In the active phases of the disease T-suppressor cell^{43,44} and natural killer cell⁴⁵ dysfunction can be seen, probably as secondary phenomena, but thymic hormones may have a therapeutic effect.⁴³ There may be two mechanisms of interferon action: antiproliferative and immune-restoring. It is interesting to note that high serum levels of interferon have been found in some cases.⁴⁵

Matsushima has demonstrated the effect of intralesional interferon by immunohistochemistry.⁴⁶ The clinical results are unequivocal. In the first published article Jakobsen reported the successful combined treatment of monozygotic twins (interferon plus steroid).⁴⁷ One of the patients had systemic disease with liver and bone marrow dysfunction. Both patients went into a prolonged complete remission.

Carstensen (personal communication) treated five patients, three of whom had organ dysfunction (bone marrow in two, lung and liver in the third). In two cases significant improvement was observed, while in a third, disease stabilisation was achieved with interferon plus high-dose prednisolone. Two patients deteriorated. Sato found that disseminated manifestations of the disease disappeared quickly in two patients,⁴⁸ while Takemari reported successful combination treatment (interferon plus etoposide).⁴⁹ Transient improvement of an adult patient was reported by Bellemunt,⁷ but Halton's monozygotic twin patients showed no response.⁵⁰ The present authors used interferon to treat a disseminated form of the disease with bone marrow dysfunction (manuscript in preparation). Through chemotherapy (prednisolone, vinblastin) a bone manifestation had appeared, leading to fracture of the right femur neck. The fracture healed rapidly on interferon therapy and the patient achieved a near-complete remission in three months.

The immune functions (T suppressor and natural killer cell activity) improve more or less in parallel with clinical improvement.⁷ In the successful cases interferon doses were 2–3 MU/m² daily. The therapeutic efficacy of interferon is very difficult to assess in Langerhans cell histiocytosis on the basis of case

Interferon: side-effects

Acute

- flu-like symptoms (in almost every case at doses usual for haematological disorders)

Chronic

- neutropenia
- thrombocytopenia
- seizures
- autoimmune phenomena
- hair loss
- growth retardation (?)

Box 3

Learning points

- interferons have antiproliferative, differentiation-inducing and immunomodulatory activity
- the results of interferon therapy in adult-type chronic myeloid leukaemia in children are similar to those in adulthood
- using very high doses in relapsing lymphoblastic disorders, a few remissions are observed of short duration
- interferon induces graft-versus-leukaemia-like reactions after bone marrow transplantation
- interferon may operate as an antiproliferative and immunorestoring agent in Langerhans cell histiocytosis

Box 4

reports, because of the spontaneous fluctuating course of the disease. However, the randomised study of the Pediatric Oncology Group has been discontinued.

Side-effects of interferon therapy

Acute side-effects in children are substantially identical to those in adults. Using interferon in a dose which is usual for haematological disorders, the well-known flu-like symptoms occur in almost every case, but they are controllable with antipyretics. Other acute side-effects are rare.⁵⁷ With the application of very high daily doses (20–50 MU/m²) it has been found that the maximum tolerated dose of children is generally higher than that of adults.³⁶ A limited experience has accumulated regarding chronic side-effects. Early fears of children’s growth retardation have not been proven,⁵² but the effect on immunological maturation is not yet known. This may be important as interferon therapy can activate latent autoimmune disease⁵³ and transient autoimmune reaction in childhood has also been reported.⁵⁴

Of the neuropsychiatric problems encountered in adults, seizures are of particular importance in children. The cause–effect relationship, however, is often not apparent.⁵⁵ Neutropenia and thrombocytopenia are important haematological side-effects; the former is frequently dose-limiting. This was the case in our own patient with Langerhans cell histiocytosis. The neutropenia was dependent upon the interferon dose and substantially lessened with commencement of steroid combination. It was unlikely that the underlying disease was responsible for the low granulocyte count, given the course of the disease. The effect of the previous cytostatic drugs, however, cannot be ignored as interferon generally causes neutropenia in such cases.⁵⁶

Discussion

The exact indications and dosages of interferon to be used in childhood malignancies remain unclear. On the basis of results with adults, it seems likely to prove to be effective in at least some of the less common diseases; good results have been achieved in adults with idiopathic hypereosinophilic syndrome,⁵⁷ and angioimmunoblastic lymphadenopathy,⁵⁸ although there are some malignancies where interferon usually shows no activity (eg, acute myeloid leukaemia, Hodgkin’s disease).

It also remains to be determined whether or not interferon can be added to current chemotherapy protocols without significant dose reduction. Ochs found the chemotherapy protocol for relapse of acute lymphoblastic leukaemia feasible, even with high doses of interferon.³⁵ Previously, based on *in vitro* data, a three times weekly dosage regime was suggested. More recently, daily administration has been suggested for patients with chronic myeloblastic leukaemia. More data are required on the metabolism and bioavailability of interferon under different conditions before definite recommendations can be made.

Long-lasting interferon therapy has a considerable cost. Health insurances cover these expenses to a highly variable degree in different diseases in different countries. This must be taken into account before starting therapy. Manufacturer-sponsored clinical trials should be welcomed to elucidate the indications and dosages of this important agent.

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