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Treatment-related deaths in second complete remission in childhood acute myeloid leukaemia

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Summary

The frequency and causes of treatment-related deaths (TRD) in second complete remission (CR2) in acute myeloid leukaemia (AML) were investigated in a historical, prospective cohort study of 429 children included in the Nordic Society of Paediatric Haematology and Oncology (NOPHO)-AML-88 and -93 trials. Relapse occurred in 158 children (39%). Seventeen (18%) of the 96 patients entering CR2 suffered TRD. The main causes were infection (59%) and complications from graft-*versus*-host disease (22%). Fourteen (82%) of 17 TRDs occurred in children undergoing haematopoietic stem cell transplantations (HSCT). Optimal supportive care after HSCT is essential, and studies on risk factors for TRD are needed.

Keywords: acute myeloid leukaemia, children, treatment-related mortality, relapse, infection.

Received 29 October 2010; accepted for publication 24 November 2010

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Presentation of the study: none.

In recent decades, treatment results for childhood acute myeloid leukaemia (AML) have constantly improved, with remission rates reaching 70–94% and survival rates exceeding 60% (Kaspers & Creutzig, 2005; Tsukimoto *et al*, 2009). The main cause of treatment failure is relapse, occurring in 30–40% of patients, even in those studies reporting the highest cure rates. Previous studies from the Nordic Society of Paediatric Haematology and Oncology (NOPHO) and other paediatric AML groups have shown that intensive treatment is associated with a very high frequency (5–15%) of deaths shortly after diagnosis or in first complete remission (CR1) (Riley *et al*, 1999; Creutzig *et al*, 2004; Rubnitz *et al*, 2004; Slats *et al*, 2005; Molgaard-Hansen *et al*, 2010). Although the number of patients treated for relapse is high, treatment-related deaths (TRD) in second complete remission (CR2) have not previously been thoroughly investigated.

The aim of the present study was to report the frequency and causes of TRDs in CR2 in childhood AML in the Nordic countries.

Patients and methods

Eligibility

Since July 1984, all children diagnosed with AML in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) have been registered and treated according to protocols conducted by the NOPHO-AML Study Group. Enrolment is population-based for patients younger than 15 years of age and follows local practice for 15- to 18-year-olds.

Patients diagnosed between 1 May 1988 and 31 December 2003 were identified in the database and were eligible for this historical, prospective cohort study. Excluded were patients treated according to other protocols than the NOPHO-AML-88/93 or pre-treated with cytostatic drugs for more than 14 d, patients with myeloid leukaemia of Down syndrome, Fanconi anaemia, Kostmann syndrome, extramedullary myeloid tumour without significant bone marrow involvement, preceding myelodysplastic syndrome or therapy-related AML.

First published online 18 January 2011
doi:10.1111/j.1365-2141.2010.08554.x

A total of 429 patients fulfilled the inclusion criteria. They had been diagnosed in 21 hospitals in Denmark (n = 92), Finland (n = 79), Iceland (n = 3), Norway (n = 85) and Sweden (n = 170). Allogeneic transplants had been performed in eight centres.

Methods

Data on patient and disease characteristics, including cytogenetics, response to therapy and treatment specifics, were collected from the Nordic AML database. The database also contains information about the time and cause of death. Seventeen TRDs in CR2 were identified. Additional data concerning these deaths were collected by reviewing the medical record of each patient using a specific registration form. Because of the low number of TRDs in CR2, multivariate analysis for possible risk factors was not attempted and only descriptive statistics are reported.

Thirty-three children had a second relapse of which four entered third complete remission (CR3). One patient suffered TRD due to an infection after chemotherapy. The three remaining patients were alive in CR3.

NOPHO-AML-88/93 treatment

The NOPHO-AML-88 and -93 protocols included cytarabine, anthracycline, 6-thioguanine and etoposide. Intrathecal methotrexate was the only central nervous system therapy given. Allogeneic haematopoietic stem cell transplantation (HSCT) in CR1 was recommended for all patients with a human leucocyte antigen (HLA)-matched family donor. For patients without a donor, autologous HSCT was optional in the NOPHO-AML-88 and the first part of the -93 protocol, and it was therefore performed on a non-randomized basis at the discretion of the responsible physician. Details concerning treatment elements, cumulative doses and clinical outcome have been reported previously (Lie *et al*, 2005).

No uniform strategy for the management of relapse was recommended in the NOPHO-AML-88/93 protocols. Management was at the discretion of the treating physician (Abrahamsson *et al*, 2007). Accordingly, relapse regimens varied between the different institutions and time periods. The main groups of treatment were: (i) NOPHO reinduction (cytarabine, 6-thioguanine, etoposide and doxorubicin), (ii) FLAG (fludarabine, cytarabine and granulocyte-colony-stimulating factor) possibly combined with an anthracycline, (iii) MACE (amsacrine, cytarabine and etoposide) and (iv) miscellaneous treatment. Allogeneic or autologous HSCT was recommended for all children in CR2.

Definitions

The diagnosis of AML was established by morphological analysis of bone marrow aspirates according to the French-American-British (FAB) and World Health Organization classifications. Complete remission (CR) was defined according to the Cancer and Leukaemia Group B criteria (Cheson *et al*, 1990).

Treatment-related death (TRD) was defined as death unrelated to progressive disease occurring after day 42 of treatment initiation in patients who achieved CR. In the present study only TRDs in CR2 are reported.

Infections were categorized as clinically, radiologically or microbiologically documented. Viral disease was registered when both relevant disease symptoms and virus were detected. Fungal infections were defined as proven invasive infection (positive histopathological findings or positive culture) (Ascioglu *et al*, 2002).

Results

By February 2010, 158 children (37%) had relapsed a median of 324 d after CR1. Table I reports patient characteristics in relation to outcome. In 20 cases (12%), care had not been aimed at achieving CR2 (Fig 1). Reinduction had been attempted in 80% of cases.

Ninety-six (76%) of the 126 children receiving reinduction entered CR2. Treatment in CR2 varied: 32 children (33%) were treated with chemotherapy only, three (3%) received an autologous HSCT and 61 (64%) an allogeneic HSCT. Three patients were transplanted with autologous HSCT in CR1 and allogeneic HSCT in CR2. The median follow-up was 10·8 (range 5·1–20·6) years for patients alive in CR2.

Frequency of TRD

The number of TRDs in the NOPHO-AML-88/93 protocols was 17 (18%) among 96 patients entering CR2. TRD percentage was 20% (3/15) in the NOPHO-AML-88 and 17% (14/81) in the NOPHO-AML-93 protocol.

Cause of TRD

Patient characteristics are shown in Table II. TRD was caused by infection in 10 (59%) of 17 cases; two bacterial, two fungal, two viral infections; in four cases the infection was only clinically or radiologically documented. Four TRDs (22%) were caused by graft-*versus*-host disease (GVHD), mainly due to pulmonary complications.

Four patients treated with allogeneic HSCT had died from TRD more than 1 year after treatment cessation. Four (24%) of the 17 patients had only been treated with chemotherapy in CR2. The remaining 13 patients had had an allogeneic HSCT, 10 (77%) using an unrelated donor.

Discussion

This is the first systematic study of TRDs in CR2 in childhood AML. The main finding was that 18% of the 96 patients entering CR2 suffered TRD. The causes were mainly infection (59%) and complications from GVHD (22%).

Table I. Characteristics of patients relapsing, dying after relapse, suffering TRD in CR2 and patients alive in CR2.

	All patients		First relapse		Death after relapse*		TRD in CR2		Alive in CR2	
	n = 429	%	*n* = 158	%	*n* = 112	%	*n* = 17	%	*n* = 45	%
Sex										
Female	216	50	79	50	53	47	10	59	26	58
Male	213	50	79	50	59	53	7	41	19	42
Cytogenetics										
Normal	88	20	30	19	20	18	6	35	9	20
Cytogenetic favourable†	94	22	21	13	9	8	3	18	12	27
Other MLL than t(9;11)	31	7	16	10	13	11	3	18	3	7
Others	136	32	53	34	39	35	4	23	14	31
No data	80	19	38	24	31	28	1	6	7	15
Protocol										
NOPHO-AML-88	114	27	39	25	34	30	3	18	5	11
NOPHO-AML-93	315	73	119	75	78	70	14	82	40	89
Consolidation in CR1										
Chemotherapy	299	70	112	71	71	63	15	88	40	89
Autologous HSCT	40	9	20	13	19	17	1	6	1	2
Allogeneic HSCT	90	21	26	16	22	20	1	6	4	9
Age relapse (years)										
<2	–	–	15	9	11	10	1	6	4	9
2–9	–	–	79	50	59	52	6	35	20	44
≥10	–	–	64	41	42	38	10	59	21	47
Time to relapse										
Early (<1 year in CR1)	–	–	88	56	71	63	9	53	17	38
Late (≥1 year in CR1)	–	–	70	44	41	37	8	47	28	62
Relapse site										
Isolated BM	–	–	137	87	94	84	16	94	42	93
BM + CNS	–	–	3	2	1	1	0	0	2	5
CNS	–	–	11	7	11	10	1	6	0	0
Extramedullary	–	–	7	4	6	5	0	0	1	2
Induction regimen for relapse										
No reinduction	–	–	20	13	20	18	1	6	0	0
NOPHO-reinduction	–	–	41	26	23	20	4	23	18	40
FLAG/FLAG+	–	–	58	37	38	34	7	41	19	42
MACE	–	–	7	4	7	6	0	0	0	0
Other	–	–	20	12	12	11	2	12	8	18
No data	–	–	12	8	12	11	3	18	0	0
HSCT in CR2										
No	–	–	32	33	23	46	4	24	9	20
Yes	–	–	64	67	27	54	13	76	36	80
Autologous HSCT	–	–	3	5	3	11	0	0	0	0
Allogeneic HSCT	–	–	61	95	24	89	13	100	36	100
Status after allogeneic HSCT in CR2 according to age:										
Age <10 years at relapse	–	–	–	–	15	42‡	5	33§	21	58‡
Age ≥10 years at relapse	–	–	–	–	9	38‡	8	89§	15	60‡

TRD, treatment-related death; CR2, second complete remission; HSCT, haematopoietic stem cell transplantation; BM, bone marrow; CNS, central nervous system; NOPHO reinduction, cytarabine, etoposide, thioguanine and doxorubicin; FLAG, fludarabine, cytarabine and granulocyte-colony-stimulating factor; FLAG+, FLAG with idarubicin or liposomal daunorubicin; MACE, amsacrine, cytarabine and etoposide.

*Includes death from progressive disease after second or third relapse and treatment-related deaths in second or third complete remission. One patient is alive in CR3 and not included in this group.

†Favourable cytogenetics: t(8;21)(q22;q22), t(9;11)(p22;q23), t(15;17)(q22;q12-21), inv16(p13q22) and t(16;16)(p13;q22).

‡Calculated in relation to all patients receiving an allogeneic HSCT in the agegroup. The number of transplanted <10 years = 36 patients. The number of transplanted ≥10 years = 24 patients.

§Calculated in relation to all deaths after relapse in the age group.

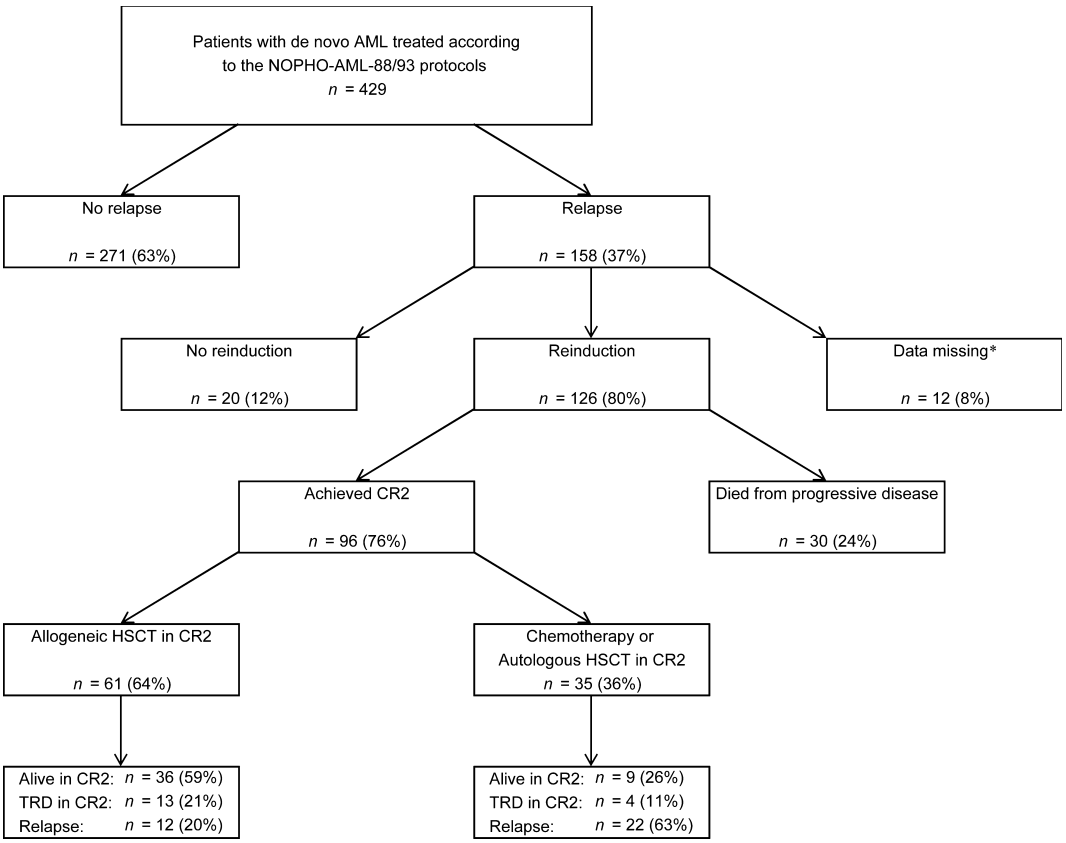

Fig 1. Flow diagram of the study population at 30 June 2007. *All died from progressive disease without achieving CR2. CR2, second complete remission; TRD, treatment-related death.

A few other paediatric AML groups have previously reported briefly on treatment-related mortality after relapse: 14% in the Medical Research Council (MRC) AML 10 trial (Webb *et al*, 1999), 14% in three consecutive protocols of the AML-Berlin/Frankfurt/Muenster Study Group (AML-BFM 87/93/98) (Sander *et al*, 2010) and 41% in three consecutive protocols from 1987 to 2002 at St. Jude Children's Research Hospital (Rubnitz *et al*, 2007). In the Leucémie Aiguë Myéloïde Enfant (LAME) 89/91 protocol, 9% of relapsed patients died from treatment-related complications after the first induction course and 15% after HSCT (Aladjidi *et al*, 2003). Based on these studies and our results, TRD in relapsed AML is considerable. However, it was difficult to compare the frequency of death between studies as definitions of TRD differed or were not offered at all.

Infection was the main reason for TRD in CR2 in our study. This rate is comparable to the one reported in the MRC-AML-10 trial (Webb *et al*, 1999). No children died of cardiac failure although relapse treatment included further anthracyclines in most cases. Four patients died from late effects related to HSCT one to 7 years after treatment had ended, stressing the importance of continued long-term follow-up. Most TRDs occurred after HSCT in our study; this is comparable to findings reported in other studies (Webb *et al*, 1999; Rubnitz *et al*, 2007). The major reason for failure after HSCT in CR2 was relapse (67%) for patients <10 years of age and TRD (89%) for patients ≥10 years (Table I).

Our study has a number of limitations. Information concerning reinduction treatment was lacking in some patients. In some cases, it was difficult to assess whether the patient was in CR and to determine whether the cause of death was disease- or treatment-related. Due to the small number of patients with relapsed AML and the diversity of regimens administered, we could not perform statistical analyses of risk factors for TRD.

The number of TRDs in CR2 in childhood AML in the Nordic countries was substantial. The frequency was however not as high as expected when comparing with the number of TRDs in CR1 (Molgaard-Hansen *et al*, 2010). Most TRDs in CR2 occurred in patients treated with allogeneic HSCT; 21% died from TRDs compared with only 11% of patients treated with chemotherapy or autologous HSCT. This is, however, counterbalanced by fewer deaths from relapse; 59% of children remain alive in CR2 after allogeneic HSCT whereas 26% of the patients treated with chemotherapy or autologous HSCT were alive. It is, however, important to continue to reduce the transplantation-related toxicity and this may be achieved with better matching of donors. The development of targeted and more leukaemia-specific drugs may also reduce the toxic effect on normal cells and thereby reduce infection-related morbi-

Table II. Characteristics of patients suffering treatment-related death in CR2 in NOPHO-AML-88/93 protocols.

Patient no.	Year of diagnosis	Age at diagnosis	Sex	Cytogenetics	FAB	Initial AML treatment	Type of relapse	Time of relapse* (months)	Relapse treatment	Survival after relapse (months)	Cause of death (Contributing cause)
1	1989	2 years	M	46,XY	M1	Full NOPHO-AML-88 protocol	BM	3	No reinduction. Allo-HSCT, MFD, conditioning Bu+Cy	3	Infection with brain abscesses, candida
2	1990	14 years	F	ND	M1	Full NOPHO-AML-88 protocol	BM	20	NOPHO reinduction Allo-HSCT, MUD, conditioning TBI+Cy	11	Infection, aspergillus
3	1992	13 years	F	46,XX,inv16(p13q22)	ND	Full NOPHO-AML-88 protocol	BM	18	Reinduction ND Allo-HSCT, MUD, conditioning Bu+Cy	11	Pneumonia, aspergillus (Lung GVHD)
4	1995	6 years	M	46,XY	M2	Full NOPHO-AML-93 protocol	BM	14	Reinduction ND Allo-HSCT 2x due to graft rejection, MUD, 1st conditioning melphalan+TBI, 2nd Cy	10	Pneumonia, adenovirus (Graft rejection)
5	1996	11 years	M	46,XY	M4	NOPHO-AML-93 protocol Auto-HSCT after 2nd consolidation	BM	5	FLAG Allo-HSCT, CBT, conditioning melphalan+fludarabine+TBI	7	Lung GVHD
6	1996	13 years	M	48,XY,+X,+11	M5	Full NOPHO-AML-93 protocol	BM	10	Reinduction ND Allo-HSCT, MUD, conditioning Bu+Cy	21	Lung GVHD
7	1997	14 years	M	46,XY,inv16(p13q22)	M4	Full NOPHO-AML-93 protocol	BM	16	NOPHO reinduction. Allo-HSCT, MUD, conditioning ND	8	Pneumonia, cytomegalovirus
8	1998	12 years	F	47,XX,+6,t(2;14)	M2	NOPHO-AML-93 protocol Allo-HSCT after 1st consolidation, MFD, conditioning cytarabine+TBI	BM	19	FLAG Six times donor lymphocyte infusion	36	Lung GVHD
9	1999	4 months	F	46,XX, t(2;8)(p13;p21), t(2;10)(q35;p12), der(10)t(10;11)(p12;q23)	M5a	Full NOPHO-AML-93 protocol	BM	12	NOPHO reinduction	3	Sepsis, streptococcus mitis
10	1999	5 years	F	46,XX, t(11;19)(q23;q13)	M5b	Full NOPHO-AML-93 protocol	BM	7	FLAG, daunorubicin. Allo-HSCT, MFD, conditioning ND	96	Lung GVHD (Cardiomyopathy)

Table II. (Continued).

Patient no.	Year of diagnosis	Age at diagnosis	Sex	Cytogenetics	FAB	Initial AML treatment	Type of relapse	Time of relapse* (months)	Relapse treatment	Survival after relapse (months)	Cause of death (Contributing cause)
11	1999	9 years	F	46,XX, t(11;17)(q23;q25)/ 46,idem,add(10)(p11)	M5	Full NOPHO-AML-93 protocol	BM	18	FLAG. Allo-HSCT, MUD, conditioning ND	22	Sepsis, streptococcus
12	1999	9 years	M	45X,-Y,add(12) (p11),-14,+mar	M4	Full NOPHO-AML-93 protocol	BM	6	NOPHO reinduction	2	Typhlitis, no positive culture
13	2000	9 years	F	46,XX	M1	Full NOPHO-AML-93 protocol	BM	7	FLAG. Allo-HSCT, MUD, conditioning Bu+Cy	72	Anoxic brain damage (Epilepsy)
14	2000	14 years	F	46,XX	M2	Full NOPHO-AML-93 protocol	BM	3	FLAG. Allo-HSCT, MUD, conditioning Bu+Cy	4	CNS bleeding
15	2001	2 years	F	Complex aberrations	M0	Full NOPHO-AML-93 protocol	BM	9	FLAG, AMSA, vepesid and cytarabine x2 Allo-HSCT x3 due to graft rejection, MUD, 1st conditioning Bu+Cy, 2nd fludara+TBI, 3rd fludara+campath+TBI	5	Sepsis, no positive culture (Graft rejection)
16	2001	2 years	M	47,XY,+8,t(9;11)(p22;q23)	M2	Full NOPHO-AML-93 protocol	CNS	During treatment	Intrathecal triple therapy was given 1 per week for 4 weeks	1	Sepsis, no positive culture (Brain damage)
17	2002	2 years	F	46,XX	M2	Full NOPHO-AML-93 protocol	BM	1	FLAG x2. Allo-HSCT, MFD, conditioning Bu+Cy	5	EBV-induced lymphoproliferative disorder

M, male; F, female; ND, no data; auto-HSCT; autologous haematopoietic stem cell transplantation; allo-HSCT, allogeneic haematopoietic stem cell transplantation; BM, bone marrow; CNS, central nervous system; NOPHO-reinduction was ATEDox (cytarabine, etoposide, 6-thioguanine, doxorubicin); MFD, matched family donor; Bu, busulfan; Cy, cyclophosphamide; MUD, matched unrelated donor; TBI, total body irradiation; CBT, cord blood transplantation; FLAG, fludarabine, cytarabine and G-CSF; AMSA, amsacrine; GVHD, graft-*versus*-host disease.
*Is given as time after end of treatment.

dity. Finally, the identification of possible risk-factors for TRD in CR2 will be useful in risk-adapted and individualized supportive care.

Acknowledgements

Research support (alphabetically): The A. P. Møller Foundation for the Advancement of Medical Science. The Aarhus University Hospital Research Initiative Foundation. The Aase and Ejnar Danielsen Foundation. The Anders Hasselbalch Foundation. The Bent Bøgh and Wife Inge Bøgh Foundation. The Carl J. Beckers Foundation. The Dagmar Marshall Foundation. The Danish Cancer Society. The Danish Childhood Cancer Foundation. The Danish Graduate School in Clinical Oncology. The Eva and Henry Frænkel Foundation. The Frode V. Nyegaard and Wife Foundation. The Johannes Fogh-Nielsen and Wife Ella Fogh-Nielsen Grant. The Karen Elise Jensen Foundation. The Kurt Bønnelycke and Wife Grethe Bønnelycke Foundation. The M. Brogaard and Wife Foundation. The Max and Anna Friedmann Grant. The Meta and Haakon Bagger Foundation. The Oticon Foundation. The Otto Christensen Foundation. The Simon Fougner Hartmann and Family Foundation. The Sophus Jacobsen and Wife Astrid Jacobsen Foundation. The Thora and Viggo Grove Grant. The University of Aarhus.

We thank all principal investigators of the NOPHO-AML-84/88/93 studies and the Nordic paediatric oncology centres for providing patient files for this study. *Investigators in Denmark*: S. Rosthøj/E. Østergaard, Aalborg; N. Clausen/H. Hasle/H. Schrøder, Aarhus; K. Schmiegelow/M. Yssing/C. Rechnitzer/B. Lausen, Copenhagen; N. Carlsen/M. Hejl, Odense. *Finland*: L. Hovi/M. A. Siimes/K. Vettenranta/U. Pihkala, Helsinki; M. Perkkiö/P. Riikonen, Kuopio; A. Mäkipernaa/M. Arrola/K. Parto, Tampere; T. Salmi, Turku; M. Lanning/M. Möttönen, Oulu. *Iceland*: G. Jónmundsson/J. Kristinsson, Reykjavik. *Norway*: S. Lie/A. Glomstein/B. Zeller/H. Glosli, Oslo; M. Hellebostad, Ullevaal; J. Helgestad/B. Moström, Bergen; S. Kolmannskog/R. Nygaard/B. Lund, Trondheim; T. Stockland/T. Flaegstad, Tromsø. S*weden*: L. Mellander/J. Abrahamsson, Gothenburg; M. Behrendtz, Linkoping; J. Heldrup/S. Garwicz/L. Hjorth, Lund; G. Gustafsson/S. Soderhall/M. Heyman, Stockholm; E. Forestier/K. Johansson/P. Sandström, Umeå; A. Kreuger/G. Lönnerholm/B. M. Frost/J. Palle, Uppsala.

Authorship

Lene Molgaard-Hansen and Henrik Hasle participated in the design of the study, provided clinical data, handled the data and drafted the manuscript.

Merja Möttönen, Heidi Glosli, Guðmundur K Jónmundsson and Jonas Abrahamsson provided clinical data in their capacity as national coordinators of this study and they participated in the interpretation of the data. All authors read and approved the final manuscript.

Conflicts of interest

None.

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