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SUPPLEMENT

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SUPPLEMENT 3.

TREATMENT PROTOCOL USED IN THE STUDY POPULATION

Acute lymphoblastic leukemia (ALL)

BFM (Berlin – Frankfurt – Münster) protocols

In total nine study participants diagnosed with ALL were treated only according to the BFM protocols. The protocol version (BFM–90, 95, 98 and 2000) was selected according to the time period the leukemia was diagnosed. Five out of 9 patients were stratified as a Standard–risk (SR) patients and treated appropriately (see below). Three were assigned to the Intermediate Risk (IR) group. One participant was treated as a High–risk (HR) patient and proceeded to hematopoietic stem cell transplantation.

BFM–90 protocol

SR and IR groups. Induction/Consolidation: seven days of prephase with increasing dose of Prednisolone and intrathecal (i.th.) MTX was mandatory, followed by oral Prednisolone 60/mg/m^2/d, for 21 days, then tapered; weekly VCR 1.5 mg/m^2 (max. 2.0 mg) concomitantly with Daunorubicine 30 mg/m^2/d i/v infusion, four doses, (8–29 d.); L–Asparaginase (Medac) 10 000 UI/m^2 i/v infusion, 8 doses, every 2–3 days (12–33 d). Cyclophosphamide 1000 mg/m^2 i/v infusion on d. 36 and 64; four blocks of four days of Cytarabine 75 mg/m^2/d, subcutaneously (d. 38–62), and oral 6–mercaptopurin 60 mg/m^2/d, given in the evening (d. 36–63); i.th. MTX on d. 1, 15, 29, 45, 59. Extra i.th. MTX on d. 8 and 22 for patients with CNS involvement. **Extra–compartment therapy (M protocol)** for SR and IR: MTX 1.0 g/m^2/24 h infusion with concomitant i.th. MTX on d. 8, 22, 36, 50; oral 6–Mercaptopurine (6–MP) 25 mg/m^2/d. (d. 1–57). **Reintensification (Protocol II):** the same as Indtuction/Consolidation except that: (i) Adriamicin was given instead of Daunorubicine; (ii) L–Asparaginase only 3 doses given; (iii) Cyclophosphamide was given once, on d. 36; (iv) Cytarabine two blocks instead of four; (v) oral 6–Thioguanine 60 mg/m^2/d instead of 6–MP on d. 36–49 and (vi) i.th. MTX on d. 38 and 45 only. **Maintenance** with oral 6–MP 50 mg/m^2/d and oral MTX 20 mg/m^2/dose, once per week with doses adjusted according to peripheral blood counts up to two years after diagnosis. IR patients older than 1.0 year additionally received **cranial irradiation** 12 Gy before maintenance.

HR patients started block therapy after the 33 d. of Induction. **Block HR–1:** oral Dexamethasone 20 mg/m^2/d (d. 1–5); oral 6–MP 100 mg/m^2/d (d. 1–5); Vincristine 1.5 mg/m^2/d (max 2.0 mg) (d. 1, 6); MTX 1.0 g/m^2/24 h infusion (d. 1); Cytarabine 2.0 g/m^2/dose, x 2 (d. 5); L–Asparaginase 25 000 IU/m^2 (d. 6); i.th. TIT (d. 1). **Block HR–2:** oral Dexamethasone 20 mg/m^2/d (d. 1–5); oral 6–TG 100 mg/m^2/d (d. 1–5); Vindesine 3.0 mg/m^2/d (max 5.0 mg) (d. 1); MTX 1.0 g/m^2/24 h infusion (d. 1); Daunorubicine 50 mg/m^2/d (d. 5); Ifosfamide 400 mg/m^2/d i/v infusion (d. 1–5); L–Asparaginase 25 000 IU/m^2 (d. 6); i.th. TIT (d. 1). **Block HR–3:** oral Dexamethasone 20 mg/m^2/d (d. 1–5); Cytarabine 2.0 g/m^2/dose, x 2 (d. 1, 2); VP–16 150 mg/m^2/dose (d. 1, 3, 5); L–Asparaginase 25 000 IU/m^2 (d. 6); TIT (d. 1). Blocks were consequently repeated three times making nine HR blocks altogether. **Maintenance** with oral 6–MP 50 mg/m^2/d and oral MTX 20 mg/m^2/dose, once per week with doses adjusted according to peripheral blood counts up to two years after diagnosis. **Cranial irradiation**: for ≥ 1.0 year patients 12 Gy after the 3rd HR–3 block.

For all risk groups patients with initial CNS involvement cranial irradiation was given dependent on age: < 1.0 y. 0 Gy; 1 –< 2.0 y. 18 Gy, and ≥ 2.0 y. 24 Gy.

BFM–95

The treatment was the same as in previous protocol except that: (i) L–Asparaginase dose was redused to 5 000 UI/m^2; (ii) HR blocks were reduced from nine to six blocks; (iii) cranial irradiation for patients with initial CNS involvement was reduced to: –< 2.0 y. 12 Gy, and ≥ 2.0 y. 18 Gy.

BFM–98

The treatment was the same as in BFM–95 protocol except that: (i) the dose of high dose MTX was increased from 1.0 g/m^2/24 h to 5.0 g/m^2/24 h; (ii) Adriamycine was replaced by Daunorubicine in Reintensification (Protocol II); (iii) prophylactic cranial irradiation was restricted only for T–ALL.

BFM–2000

The treatment was the same as in BFM–98 protocol except that: (i) the dose of high dose MTX was increased from 1.0 g/m^2/24 h to 5.0 g/m^2/24 h; (ii) Adriamycine was replaced

by Daunorubicine in Reintensification (Protocol II); (iii) prophylactic cranial irradiation was restricted only for T–ALL.

NOPHO ALL–92 AND ALL–2000 THERAPY STRATEGY

The only study participant treated according to NOPHO–2008 protocol was treated according to the IR group.

Details of the NOPHO ALL–92 and –2000 protocols are in detailed described in the NOPHO group publications {Vaitkeviciene, 2011 100 /id;Schmiegelow, 2010 137 / id;Gustafsson, 2000 145 /id}.

Induction therapy: In ALL–92 all patients received prednisolone (60 mg/m^2/day on days 1–36, then tapered), weekly vincristine (VCR) (2.0 mg/m^2 six times, maximum 2.0 mg), doxorubicin (40 mg/m^2 three times (SR and IR) or 4 times (HR)), Erwinia asparaginase (30.000 IU/m^2 daily on days 37–46), and intrathecal (i.t.) methotrexate (MTX) on four occasions. ALL–2000 induction therapy was identical to that of the ALL–92 protocol except that i) one dose less of doxorubicin was given, ii) the maximum dose of VCR was set to 2.5 mg, and iii) Erwinase was substituted with E–coli asparaginase (6.500 IU/m^2 at three days intervals, times 4).

Early intensification consisting of cyclophosphamide (1000 mg/m^2 times 2, four weeks apart), i.t. MTX, oral 6–mercaptopurine (6–MP) and low–dose cytarabine (75 mg/m^2/day for four days, times 4), was given to IR and HR patients immediately after the induction phase.

Consolidation therapy in ALL–92 included high–dose MTX (HD–MTX) at 5 g/m^2/24 hours for SR and IR with i.t. MTX and Leucovorin rescue, whereas patients with higher risk–ALL received HD–MTX 8 g/m^2/24 hours alternating with high–dose cytarabine (12 g/m^2) with 2–month intervening periods of oral MTX and 6–MP with two VCR/prednisolone reinductions per period (163). In ALL–2000, SR and IR patients received three HD–MTX courses alternating with low–dose cytarabine blocks (75 mg/m^2/day for four days, times 2) with concomitant 6–MP, whereas HD–MTX consolidation therapy for higher risk patients was identical to that of the ALL–92 protocol. ***Delayed intensification*** in both ALL–92 and ALL–2000 was given to IR and higher risk patients and consisted of oral dexamethasone, weekly VCR four times, weekly anthracycline 3 or 4 times and 4 doses of asparaginase given twice weekly (Erwinia asparaginase in ALL–92, E–coli asparaginase in ALL–2000), followed by cyclophosphamide at 1000 mg/m^2, low–dose cytarabine and 6–thioguanine (106, 164).

Classical oral 6–MP/MTX ***maintenance therapy*** continued until 2 years (for IR and HR in ALL–92 and for HR and VHR in ALL–2000) or 2.5 years (for SR in ALL–92 and for SR and IR in ALL–2000) after diagnosis. During the first year of maintenance therapy SR or IR–ALL received in addition alternate pulses at four weeks intervals of VCR and corticosteroids and HD–MTX at 5 g/m^2/24 hours until five courses of HD–MTX had been given. HR and VHR received reinductions of VCR and corticosteroids. In ALL–92 patients with VHR ALL (and all Finish patients with HR ALL) had oral 6–MP/MTX maintenance, substituted with cyclic LSA_2L_2 maintenance therapy, while in ALL–2000 LSA_2L_2 was given two (HR) or three times (VHR) prior to the start of oral MTX/6MP maintenance therapy, or until SCT could be performed (VHR–ALL) (106, 164)

A subset of patients with higher risk ALL was offered ***cranial irradiation*** in the ALL–92 (N = 158) and ALL–2000 (N = 128) protocols. These included very high risk ALL (VHR) patients, who were 5 years of age and older.

ACUTE MYELOBASTIC LEUKEMIA

All 3 patients were treated according to BFM protocols, two according to AML–BFM–2004 (1 SR with HSCT, and 1 HR), other – AML–BFM–98 SR.

AML–BFM–1998

For SRG patients: AIE (induction 1), HAM (induction 2), AI (consolidation), haM (intensification 1), HAE (intensification 2), prophylactic cranial radiotherapy and maintenance.

AML–BFM–2004

For HRG patients: AIE (induction 1), HAM (induction 2), AI (consolidation), haM (intensification 1), HAE (intensification 2), prophylactic cranial and maintenance.

For SRG patients: AIE (induction 1), AI (induction 2), haM (consolidation), HAE (intensification), prophylactic cranial radiotherapy, maintenance.

Block AIE: Ara C 100 mg/m^2 continued infusion (day 1 through 2), Ara C 100 mg/m^2 2x1 (days 3 through 8), VP–16 150 mg/m^2/d (days 6,7,8), idarubicine 12 mg/m^2 (days 3,5,7), intrathecalAra C in age matched dose (day 1). **Block HAM:**Mitoxantrone 10 mg/m^2 (days 3, 4), Ara C 3 g/m^2, 2x1, 6 doses, days 1 through 3); intrathecalAra C in age matched dose (day 1). **Block AI:**Idarubicine 7 mg/m^2 (days 3, 5), Ara C 500 mg/m^2 (days 1 through 5), intrathecalAra C in age matched dose (day 1,6). **Block haM:** Ara C: 1 g/m^2 2x1, 6 doses, days 1–3), mitoxantrone 10 mg/m^2 (day 3, 4), intrathecalAra C in age matched dose (day 1, 6). **Block HAE:**Ara C 3 g/m^2 2x1, 6 doses (days 1–3), etoposide 125 mg/m^2 (days 2–5), intrathecalAra C in age matched dose (day 1). **Maintenance:** Cytarabine 40 mg/m^2 consecutive 4 days every month, 6–Thioguanine 40 mg/m^2 /d for 1 year po, intrathecalAra C in age matched dose (day 1,8,15,22 beginning concomitant with CNS irradiation). **IntrathecalAra C:** < 1 y:20 mg; 1 –< 2 y: 26 mg, 2 –≤ 3 y: 34 mg, > 3 y: 40 mg). **Prophylactic cranial radiotherapy:** > 1 year of age: 12 Gy· (6).

LYMPHOMAS

Hodkin's lymphoma

Five out of 9 patients were treated according to GPOH–HD–2001, 2 – according to GPOH–HD–95 protocol.

GPOH–HD–95

Both patients got 2 OEPA blocks, 2 COPP blocks (TG2).

GPOH–HD–2001

One patient was treated according to TG1, two patients – TG2, two patients – TG2. TG1 – 2 OEPA blocks, TG2 – 2x OEPA, 2x COPDIC, TG3 – 2x OEPA, 4x COPDIC

Block OEPA: Adriamycin 40 mg/m^2/D (days 1, 15) infusion, i.v. Vincristine 1.5 mg/m^2/D on days 1, 8, 15, Etoposide 125 mg/m^2/d (days 3–6), oral Prednisolone 60 mg/m^2/d (days 1–15).

Block COPP: Cyclophosphamide 500 mg/m^2/D infusion on days 1, 8, Vincristine 1,5 mg/m^2/D on days 1,8, oral Procarbazine 100 mg/m^2/d on days 1–15, oral Prednizolone 40 mg/m^2/d on days 1–15.

Block COPDIC: Cyclophosphamide 500 mg/m^2/D infusion on days 1, 8, Vincristine 1,5 mg/m^2/D on days 1,8, Dacarbazine 250 mg/m^2 infusion on days 1–3, oral Prednizolone 40 mg/m^2/d on days 1–15.

NON HODKIN'S LYMPHOMA

Five patients were treated according to NHL–BFM–95 protocol, R2 group. One patient was treated according to BFM–ALL–2000 (T–lymphoma).

NHL–BFM–95 (R2): treatment included V, A24, B24 A24, B24 blocks.

Block V: Cyclophosphamide 200 mg/m^2/d on days 1 and 2, oral dexamethasone 5–10 mg/m^2/d on days 1–5, i.t. MTX 6–12 mg, ARA C 16–30 mg, PRED 4–10 mg, three times on day 1.

Block A24: oral Dexamethasone 10 mg/m^2/d on days 1–5, i.v. Vincristine 1.5 mg/m^2 (max. 2 mg) on day 1, VP–16 100 mg/m^2/d 2 hours infusion on days 4, 5, ARA C 150 mg/m^2 1 hour infusion two times per day, on days 4 and 5, MHD–MTX 1g/m^2 24 hours infusion on day 1, i.v. Leukovorin 15 mg/m^2 on 42, 48, 54 hours of treatment, Ifosfamide 800 mg/m^2/d 1 hour infusion three times on day 2, i.t. MTX 6–12 mg, ARA C 16–30 mg, PRED 4–10 mg, three times on day 2.

Block B24: oral Dexamethasone 10 mg/m^2/d on days 1–5, i.v. Vincristine 1.5 mg/m^2 (max. 2 mg) on day 1, doxorubicin 25 mg/m^2/d 1 hour infusion on days 4 and 5, MHD–MTX 1g/m^2 24 hours infusion on day 1, i.v. Leukovorin 15 mg/m^2 on 42, 48, 54 hours of treatment, Cyclophosphamide 200 mg/m^2/d 1 hour infusion on days 1–5, i.t. MTX 6–12 mg, ARA C 16–30 mg, PRED 4–10 mg, three times on day 2.

NEUROBLASTOMA

NB–90

Two patients were treated according to NB–90 treatment, which included surgery, radiotherapy, and blocks N1, N2, N1, N2, N1, N2, N1, N2.

Block N1: Cisplatin 40 mg/m^2/d 96 hours infusion on days 1–4, VP16 125 mg/m^2/d 96 hours infusion on days 1–4, Vindesine 3 mg/m^2/d 1 hour infusion on day 1.

Block N2: VCR 1.5 mg/m^2/d infusion on days 1 and 8, Dacarbazine 200 mg/m^2/d 1 hour infusion on days 1–5, Ifosfamide 1.5 g/m^2/d 120 hours infusion on days 1–5, Adriamycine 30 mg/m^2/d 48 hours infusion on days 6–7.