The Dutch-Belgian pediatric acute myeloid leukemia protocol for children with newly diagnosed acute myeloid leukemia (DB AML-01)

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The Dutch-Belgian acute myeloid leukemia (AML)-01 protocol for children and adolescents until the age of 19 years with newly diagnosed AML, recently opened in Belgium and the Netherlands (EudraCT nr. 2009-014462-26). It is an international single arm study consisting of 5 intensive chemotherapy courses with cytarabine-arabinoside, etoposide and anthracyclins as major components. The protocol is a modification from the Nordic Society for Pediatric Hematology and Oncology (NOPHO) AML 2004 protocol which consists of 6 chemotherapy courses and a gemtuzumab ozogamicin (Mylotarg®) postconsolidation randomisation, with a reduction in the total anthracyclins dosage in the DB AML-01 trial. This study will answer the question whether treatment with these 5 intensive courses will maintain a cumulative 3-years relapse rate of 40% or less while decreasing long term cardiotoxic effects of the treatment. The inclusion time is restricted to a maximum of 4 years and/or 120 evaluable patients. Various research studies will be performed on biological material from the registered patients.

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Background

Acute myeloid leukemia (AML) is a rare disease in children. In the Netherlands and Belgium approximately 30-35 children (ages 0-18 years) will be diagnosed with AML every year. Over the past 20 years, there has been an important improvement in therapeutic outcome of childhood AML due to treatment intensification based upon high doses of cytarabine-arabinoside (Ara-C) and anthracyclins during induction and consolidation.

Nowadays, complete remission (CR) can be achieved in 85-90% of children. However, the 5 years overall survival rate (OS) is only 50-60% due to a high relapse frequency, especially during the first and second years after diagnosis.

The results of the latest protocol of the Nordic Society for Pediatric Hematology and Oncology (NOPHO AML 1993) are among the best in Europe, with a 5 years OS of 65% and a 5 years event free survival (EFS) of 48%.[1-3] This success is attributed to the timing of the courses (i.e. starting of the second induction course at day 15 after the first

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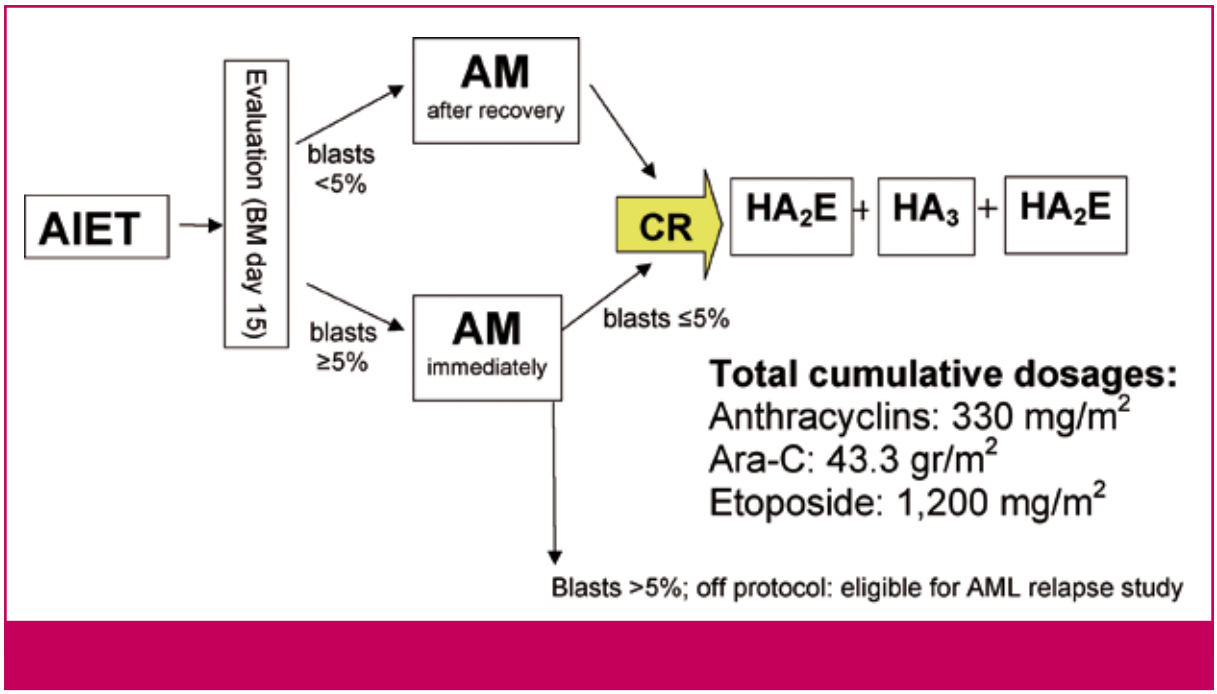

Figure 1. The Dutch-Belgian pediatric acute myeloid leukemia (DB AML-01) treatment schedule. *AIET=Ara-C + idarubicin + etoposide + 6-Thioguanin, AM=Ara-C + mitoxantrone, BM=bone marrow, CR=complete remission, HA=high dose Ara-C.*

course in patients with ≥5% residual blasts in the bone marrow) and a backbone of high total doses of Ara-C during consolidation.

Early studies established the cardiotoxic threshold for anthracyclin dose at 550 mg/m^2 in adults. In children even lower doses of anthracyclins are at risk of exhibiting subclinical cardiovascular dysfunction and clinically significant cardiomyopathy.[4,5] Currently available studies show a progressive cardiovascular dysfunction over time when treated with anthracyclin dosages over 300 mg/m^2. Altogether, these results have made us aware of possible cardiac damage in the upcoming long-term survivors after AML treatment. Therefore, the most cardiotoxic consolidation course from the NOPHO-AML 2004 trial was skipped, resulting in a decrease of anthracyclin doses from 450 to 330 mg/m^2 in DB AML-01 study protocol.

The role of allogeneic stem cell transplantation (SCT) in pediatric AML is controversial. Updates from the larger international collaborative study groups have shown no significant benefit for sibling SCT in standard risk or high risk groups.[2,3,6,7] Allogeneic SCT in the first CR is not recommended in this study protocol. Patients not achieving first CR after 2 courses of chemotherapy will be off protocol and eligible for a pediatric protocol for refractory and relapse AML. However, in patients with monosomy 7 and no CR after 2 induction courses, an SCT should be initiated.[8]

Protocol DB AML-01

The Dutch Childhood Oncology Group (DCOG) acts as overall study sponsor, whereas the DCOG and the Ghent University hospital are national sponsors for the Netherlands and for Belgium, respectively. The protocol is open for primary AML (as defined by the diagnostic criteria) in children and adolescents until the age of 19 years. Written informed consent must be obtained before registration.

Exclusion criteria are previous chemo- or radiotherapy, AML secondary to previous bone marrow failure syndromes, Fanconi anemia, Down syndrome below the age of 5 years, Down syndrome patients of any age with *GATA1* mutation, acute promyelocytic leukemia, juvenile myelomonocytic leukemia and myelodysplastic syndrome.

The overall treatment schedule is shown in *Figure 1*. Patients are treated with 2 induction courses (AIET and AM) and 3 consolidation courses (HA_2E, HA_3, HA_2E).

High risk patients are defined by the presence

of at least 15% of blasts in the day 15 bone marrow after the first induction course but in CR after the second induction course, and no favorable cytogenetics (t(8;21)(q22;q22), inv(16)(p13q22)/t(16;16)(p13;q22)).

The AIET course consists of 6-Thioguanin 100 mg/m²/12 hrs orally (day 1,2,3,4) + Ara-C 200 mg/m²/d continuous IV infusion (day 1,2,3,4) + etoposide 100 mg/m²/d continuous IV infusion (day 1,2,3,4) + idarubicin 12 mg/m² as a 4-hour IV infusion on day 2, 4, and 6. The AM course consists of Ara-C 100 mg/m²/d as continuous IV infusion for 5 days + mitoxantrone 10 mg/m² as a 30-minute IV infusion on day 1,2,3.

In the consolidation courses, high dose Ara-C is given (12 g/m² in HA_2E and 18 g/m² in HA_3), in combination with etoposide 100 mg/m² as a 60-minute IV infusion day 2,3,4,5 in course HA_2E.

All patients receive one triple intrathecal injection (with age-adjusted doses) in each course as CNS directed therapy. In addition, patients with CNS involvement at initial diagnoses are treated with multiple intrathecal injections as described in the protocol.

Rigorous supportive care should be implemented for the total duration of the treatment and all serious adverse events, as defined in the protocol, occurring in a subject during diagnostics and treatment should be reported to the DCOG Trial Office within 48 hours.

Additional information on the DB AML-01 protocol can be found in the Dutch Trial Register ('Nederlands Trial Register'; NTR2120) and on the websites of the DCOG and the Belgian Society for Pediatric Hemato-Oncology (BSPHO).

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