TITLE: Long-term outcome evaluation of medium-high risk acute lymphoblastic leukemia children treated with or without cranial radiotherapy in the EORTC 58832 randomized study

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Historically, pre-emptive cranio-spinal or cranial radiotherapy (CRT) was a standard component of childhood acute lymphoblastic leukemia (ALL) treatment protocols to prevent central nervous system (CNS) relapses. The emergence of CRT-related neurotoxicity, endocrine sequelae and second neoplasms (SN) prompted several authors to investigate alternative methods of CNS prophylaxis.¹ Systemic and intrathecal chemotherapy could successfully replace CRT in protocols for standard-risk ALL. However, in patients presumed to be at increased-risk of CNS relapse, the omission of CRT remains debatable.

Between 1983 and 1989, we investigated whether CRT could be omitted in a BFM-oriented protocol in which systemic and intrathecal chemotherapy was administered to prevent CNS relapses in patients aged 1 to 17 years with CNS negative *de novo* ALL, either standard-risk (study 58831), or medium/high-risk (study 58832). Stratification was based on the risk factor calculation according to Langerman *et al.*² Standard-risk patients received no CRT and were treated with 4 methotrexate (MTX) infusions at 0.5 g/m² and 6 intrathecal MTX injections (*Online Supplementary Material and Methods, Online Supplementary Figure 1*). Medium/high-risk patients still in complete remission (CR) at the end of late intensification were randomized to receive CRT (standard arm) or not (experimental arm) before the start of maintenance therapy. Prophylactic CNS therapy consisted of 4 high-dose MTX infusions (2.5 g/m²) during interval therapy and 7 intrathecal MTX injections.

In 2000, we reported the initial results of the efficacy analyses in terms of disease-free survival and incidence of CNS relapse, for both studies 58831 and 58832 at a median follow up of 9.4 years.³ Here, we provide the updated results of the randomized question comparing *No CRT* vs *CRT* in medium/high-risk patients included in study 58832, at a median follow up of 20 years (range 4-32 years). In addition to the long-term outcome, we also evaluated the incidence of SN and the rate of late adverse effects by treatment arm. Standard-risk patients included in study

58831 are not part of the present analysis, except for the evaluation of the late adverse effects after different MTX dosages.

Endpoints were disease-free survival (DFS) (event: relapse, death in CR1), incidence of any CNS and of isolated CNS relapses, incidence of SN at any stage and in CR1, event-free survival (EFS) (event: relapse without SN, SN in CR1, death in CR1 and without SN), overall survival (OS) from randomization and rate of late adverse effects (defined following the CTCAE 4.0 scale). The expected incidence of any CNS relapse in the *CRT* arm was 10% at 3 years. The trial was designed to test whether in the *No CRT* arm, compared to the *CRT* arm, the increase of the any CNS relapse incidence is <10%, i.e. the treatment hazard ratio (HR) is <2.12.

A total of 189 patients were randomized in study 58832. Among them, 176 patients were included in the present per-protocol treatment evaluation: 84 patients in the *CRT* arm and 92 patients in the *No CRT* arm (*Online Supplementary Figure 2*). Clinical characteristics were well balanced in both treatment arms (Table 1).

The 25-yr DFS rate was similar in both arms (67.4% without CRT vs 70.2% with CRT, Figure 1A, Table 1). No relapse occurred after 7 years. The 25-year incidence of any CNS relapse was 8.7% (SE 2.9%) vs 11.9% (SE 3.5%) in the *No CRT* and *CRT* arms, and the 25-year incidence of isolated CNS relapse was 6.5% (SE 2.6%) vs 4.8% (SE 2.3%) respectively (Figure 1A, Table 1). The comparison of the incidence of any CNS relapse in the patients randomly assigned to *No CRT* vs *CRT* yielded a HR of 0.71 (95% CI 0.28-1.79), significantly lower than 2.12 (test for non-inferiority: 1-sided P=0.01), indicating that the increase of the any CNS relapse incidence without CRT was lower than 10%.

Omission of CRT was associated with a decreased 25-year SN incidence at any time (7.3% without CRT vs 13.0% with CRT) and in CR1 (7.9% without CRT vs 11.0% with CRT) (Table 1).

The median time to develop SN was 23 years in the *No CRT* arm and 8.7 years in the *CRT* arm. In the *No CRT* arm, four patients (4.3%) had SN: 1 pleomorphic xanthoastrocytoma, 1 melanoma, 1 thyroid carcinoma and 1 adenocarcinoma of the ileum. In the *CRT* arm, nine patients (10.7%) developed SN: 1 malignant histiocytosis, 1 non-Hodgkin lymphoma, 1 thyroid carcinoma, 4 meningiomas and 2 acute myeloid leukemias (AML). In both AML cases, the fingerprint of a secondary leukemia (t11q23, monosomia 7, 5q-) was lacking. Second or synchronous SN were exclusively observed in patients treated with CRT, in first- or second-line treatment (*Online Supplementary Table 1*). One patient with malignant histiocytosis died of SN, all others were alive at last follow up. The 25-year EFS rate was similar in both arms: 59.5% without CRT vs 60.5% with CRT (Figure 1C Table 1) and the 25-year OS rates were similar in both arms: 78.5% and 78.1% respectively (Figure 1B, Table 1).

Omission of CRT was also associated with a dramatic decrease in the rate of late CNS adverse effects (Table 2). Leukoencephalopathy was reported in two patients (8.7%) randomized in the *No CRT* arm but previously treated with CRT or TBI in second line treatments, vs five (19.2%) in the *CRT* arm. The rate of seizures was 4-fold decreased in patients randomized to *No CRT* arm. In the *No CRT* arm, the only patient with seizures had hereditary epilepsy. In the *CRT* arm, convulsions were secondary to meningiomas (n=2) or related to bilateral subdural effusions after CNS relapse (n=1) or to severe encephalopathy occurring during CRT (n=1). Strokes (n=2) were reported only in the *CRT* arm, at 6 and 24 years after end of treatment. Finally, cognitive disturbance was reported in three patients of the *No CRT* arm (2 in CR and 1 after a BM relapse treated with CRT), corresponding to a 2-fold decreased rate.

As late neurotoxicity could also be related to high-dose MTX, we compared the rate of late adverse effects in patients randomized for *No CRT* and treated with high-dose MTX in study 58832, with that of standard-risk patients treated without CRT and with lower dosage of MTX (0.5

g/m²) in study 58831 (*Online Supplementary Figure 1*). Decrease in MTX dosage was associated with lower rates of leukoencephalopathy and cognitive disturbance (Table 2).

Finally, in study 58832, omission of CRT was associated with a decreased rate of late endocrine adverse effects (Table 2). In the *No CRT* arm, the rate of GH deficiency was reduced by more than half and no patient developed hypothyroidism and precocious puberty, versus around 30% of the patients in the *CRT* arm. The rate of delayed puberty was similar in both arms.

In conclusion, our long-term analysis of CNS negative medium/high-risk ALL patients confirms previous observations documenting a decrease in SN incidence, particularly for second CNS tumors^{4,5} and a lower rate of CNS^{6,7} and endocrine⁸ adverse effects when CRT is omitted. Noteworthy, patients randomized in the *No CRT* arm had similar 25-year incidence of any (8.7% vs 11.9%) and of isolated (6.5% vs 4.8%) CNS relapse compared to the *CRT* arm. In the initial publication of EORTC studies 58831 and 58832³, comprising 707 standard and medium/high-risk patients, the 10-year incidence of any CNS relapse was approximately 10%, and was comparable to that of the similar ALL-BFM 83 study (8.7%).⁹ In the EORTC study, only 12% received CRT in CR1 whereas in the BFM study, 70% of the patient population had to receive CRT, including the CNS-3 patients (2.9%).

The 8-year incidence of any and isolated CNS relapse progressively decreased in subsequent EORTC studies, despite the omission of CRT for all patients in CR1: 7.6% and 3.6% respectively in study 58881 (1989-1998),¹⁰ 3.7% and 1.7% in study 58951 (1998-2008).¹¹ St Jude and DCOG also omit CRT for all patients in their respective Total Therapy XV¹² and DCOG ALL-9 studies,¹³ and obtained isolated CNS relapse incidences of 2.7% and 2.6% respectively. St Jude identified small subgroups of patients at high-risk of CNS relapse, and intensify their systemic CNS prophylaxis in the current Total Therapy XVI (e.g. up to 27 intrathecal injections in standard/high-

95 risk patients at high-risk of CNS relapse). In the current EORTC treatment 58081 guidelines,
96 PEGylated asparaginase and its activity monitoring are recommended, since L-asparaginase
97 plays a role in preventing CNS relapses.¹⁰ Patients with CNS-3 status receive dexamethasone
98 during induction or receive higher cumulative dose of dexamethasone during late intensification,
99 depending on their initial risk group. Intrathecal chemotherapy ranges from 11 injections in CNS-
100 negative very low-risk patients to 22 injections in CNS-3 very high-risk patients. Long-term
101 prospective studies are still needed to evaluate the impact of intensified systemic CNS
102 prophylaxis on the neurocognitive outcome of ALL survivors ¹⁴ and optimal schedules need to be
103 established.

104 Taken together, our observations add to the body of evidence that, with proper systemic and
105 intrathecal CNS prophylaxis, CRT could totally be omitted in CR1 without jeopardizing overall
106 survival while decreasing the long-term side effects in ALL children.

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FIGURE LEGENDS

Table 1 – Distribution, (A) of the clinical and disease characteristics and of the outcome, according to the treatment arm (*No CRT* vs *CRT*) in EORTC study 58832; and (B) of the late adverse effects, according to the treatment (EORTC study 58831 and *No CRT* vs *CRT* in EORTC study 58832).

Figure 1 – (A) Kaplan-Meier curve of disease-free survival (event: relapse, death in CR1) and cumulative incidence of any CNS relapse, (B) Kaplan-Meier curve of overall survival and (C) Kaplan-Meier curve of event-free survival (event: relapse without SN, SN in CR1, death in CR1 and without SN) and cumulative incidence of SN in CR1 (C) by treatment arm (*No CRT* or *CRT*).