**JPED-2018-5410 Supplementary Material**

**Supplementary Material**

**Table S1 - Treatment protocol for standard risk patients (modified from BFM 90 protocols8).**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment phase/timing of given drug** | **Dose (route)** | | **Schedule** | | |
| **Induction (Phase I; 4 weeks)** | | | | | |
| Prednisone | 60 mg/m2 (PO) | | | 1–28 | |
| Vincristine | 1.5 mg/m2 (IV) (2 mg max) | | | 1, 8, 15, 22 | |
| Daunorubicina | 25 mg/m2 (IV) | | | 1, 8, 15, 22 | |
| L-asparaginase | 6,000 IU/m2 (IM) | | | 3, 5, 7, 9, 12, 14, 16, 19, 21 | |
| Methotrexate b | 12 mg (according to age) (IT) | | | 1, 15, 28 | |
|  |  | | | **BM assessment day 29** | |
| **Consolidation (Phase II; 4 weeks)** | | | | | |
| Cyclophosphamide | 1,000 mg/m2 (IV) | | | 1, 15 | |
| Cytarabine | 75 mg/m2(IV) | | | 2-5, 9-12, 16-19, 23-26 | |
| 6-mercaptopurine | 60 mg/m2 (PO) | | | 1-28 | |
| Methotrexate b | 12 mg (according to age) (IT) | | | 5, 12, 19, 26 | |
|  |  | | | **BM assessment day 29** | |
| **Interim Maintenance (Phase III; 8 weeks)c** | | | | | |
| Methotrexate | | 20 mg/m2 (PO) | | | Weekly (8 doses) |
| 6-mercaptopurine | | 60 mg/m2 (PO) | | | 1–56 |
| Methotrexate b | | 12 mg (according to age) (IT) | | | Day 28 |
|  | |  | | | **BM assessment day 56** |
| **Re-induction/delayed intensification (Phase IV; 8 weeks)** | | | | | |
| Dexamethasone | 10 mg/m2 (PO) | | | 1–21 | |
| Vincristine | 1.5 mg/m2 (IV) (2 mg max) | | | 1, 8, 15, 22 | |
| Doxorubicin | 30 mg/m2 (IV) | | | 1, 8, 15, 22 | |
| L. asparaginase | 10,000 IU/m2 (IV/IM) | | | 3, 5, 7, 9, 12, 14, 16, 19, 21 | |
| Cyclophosphamide | 500 mg/m2 (IV) | | | 36 | |
| Cytarabine | 75 mg/m2 (IV) | | | 38–41, 45–48 | |
| 6-thioguanine d | 60 mg/m2 (PO) | | | 36–49 | |
| Methotrexate b | 12 mg (according to age) (IT) | | | 38, 45 | |
|  |  | | | **BM assessment day 49** | |
| **Continuation/maintenance (Phase V; 12 weeks, repeated for 12 cycles)e** | | | | | |
| Prednisone | 40 mg/m2 (PO) | | | 1-14 | |
| Vincristine | 1.5 mg/m2 (IV) | | | 1, 8 | |
| 6-mercaptopurine | 75 mg/m2 (PO) | | | Daily | |
| Methotrexate | 20 mg/m2 (PO) | | | Weekly | |
| Methotrexateb | 12 mg (according to age) (IT) | | | 1 | |
|  |  | | | **BM assessment** at the end of each cycle, every 12 weeks. | |

PO, orally; IV, intravenous infusion; IT, intrathecally.

a Doxorubicin, a readily available and cheaper medication, which was administered in equivalent doses to all patients.

b Methotrexate intrathecal dose: 12 mg (> 3 years), 10 mg (2-3 years), 8 mg (1-2 years), 6 mg (< 1 years).

c Interim maintenance phase was omitted in most cases due to the prolonged duration of induction, as it entails complications such as fever, infection, severe mucositis, extravasations of chemotherapy, etc., in order to avoid delaying re-induction/intensification phase.

d Not available most of the time and not administered.

e Patients were treated as outpatients with out-patient appointments for W1,W2, and later every month to ensure their compliance and to ensure medication resupply for those in short supply.

**Table S2 - Treatment protocol for high risk patients, based on BFM 90, was Protocol I, (HR1, HR2, HR3) administered every three weeks, completing a total of nine courses, then onto the continuation phase, which was proceeded by 12 Gy of preventive cranial radiation if possible.a**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Dose** | | **Schedule days** |
| **Protocol I** | | | |
| Prednisone | 60 mg/m2 (PO) | | 1–28 |
| Vincristine | 1.5 mg/m2 (IV) | | 8, 15, 22, 29 |
| Daunorubicin b | 30 mg/m2 (IV) | | 8, 15, 22, 29 |
| L-asparaginase | 10,000 IU/m2 (IM) | | 12, 15, 18, 21, 24, 27, 30, 33 |
| Cyclophosphamide | 1,000 mg/m2 (IV) | | 36, 64 |
| Cytarabine | 75 mg/m2 (IV) | | 38–41, 45–48, 52–55, 59–62 |
| 6-Mercaptopurine | 60 mg/m2 (PO) | | 36–64 |
| Methotrexate | Dose according to age (IT) | | 1 |
| TIT | Dose according to age (IT) | | 15, 29, 45, 59 |
| **HR 1** | | | |
| Dexamethasone | | 10 mg/m2 (PO) | 1–5 |
| Vincristine | | 1.5 mg/m2 (IV) (2 mg max) | 1, 6 |
| Methotrexate c | | 2 g/m2 (24 h infusion) | 1 |
| 6-mercaptopurine | | 100 mg/m2 (PO) | 1–5 |
| Cytarabine | | 2 g/m2 every 12 h (IV) (3 h infusion) | 5 |
| L-asparaginase | | 25,000 IU/m2 (IM) | 6 |
| TIT | | Dose according to age (IT) | 1 |
| **HR 2** | | | |
| Dexamethasone | | 20 mg/m2 (PO) | 1–5 |
| Vindesine d | | 3 mg/m2 (max. 5 mg) (IV) | 1 |
| Methotrexate c | | 2 g/m2 (24 hours infusion) | 1 |
| 6-thioguanine e | | 100 mg/m2 (PO) | 1–5 |
| Ifosfamide | | 400 mg/m2 (IV, 1 hour infusion) | 1–5 |
| Daunorubicin | 50 mg/m2 (IV, 1 hour infusion) | | 1 |
| L-asparaginase | 25,000 IU/m2 (IM) | | 1 |
| TIT | Dose according to age (IT) | | 1 |
| **HR 3** | | | |
| Dexamethasone | 20 mg/m2 (PO) | | 1–5 |
| Cytarabine | 2 g/m2 every 12 hour (IV, three hour infusion) | | 1, 2 |
| Etoposide | 150 mg/m2 (IV, 1 hour infusion) | | 3, 4, 5 |
| L-asparaginase | 25,000 IU/m2 (IM) | | 6 |
| TIT | Dose according to age (IT) | | 5 |

a If cranial radiation was unavailable for CNS3 patients then TIT was administered, every other day for 12 doses, until CSF was clear.

TIT, triple intrathecal therapy, specifically ara-C, methotrexate, and hydrocortisone.

b Doxorubcin, a readily available and cheaper medication that was administered in equivalent doses to all patients.

c Omitted in some of the patients due to either the unavailability of Ca-leucovorin, lack of serum methotrexate drug monitoring, or if they suffered from presence of liver disease. If Ca-leucovorine was given, rescue was initiated: 15 mg/m2 at 36, 42, 48 and 54 hours after the start of methotrexate infusion.

d Vindestin, due to unavailability, was replaced with Vincristine.

e Not available most of the time and not administered.

IV, intravenous; IM, intramuscular; PO, orally; IT, intrathecally.

**The authors’ modifications of the BFM 90 protocol:**

**Doxorubicin was used** instead of Daunorubicin, as it was more readily available and is a cheaper medication. It was administered in equivalent doses.

**Methotrexate (MTX)** usage was limited and was mainly offered to high-risk patients and to those free from liver disease. High doses were avoided due to unavailability of rescue therapy (Ca-leucovorin) or the lack of MTX drug monitoring, especially since Egypt has the highest prevalence of hepatitis B and C in the world. It was noticed that there was a marked increase in toxic hepatitis deaths in the leukemia patients, and thus it was subsequently omitted in the years following.

After 2017, MTX was re-introduced using the escalating dose method (Cappizzi): MTX starting dose 100 mg/m 2 and escalate by 50 mg/m2/dose, which allowed the use of lower doses of MTX without rescue (Ca-leucovorin), and allowed gradually increasing the doses while monitoring any toxicities.

**L-asparagenase:** Pegulated L-asparaginase was unavailable due to its high cost. Therefore, different forms of L-asparagenase were used, specifically Escherichia coli and Erwinia; whichever of the two medications that were available would be then administered to the patient either through IM or IV. The doses also differed depending on the commercial forms of the drug that were available.

**Interim maintenance phase (phase III):** This phase was omitted from the protocol in most cases due to the prolonged duration of induction, as it entails complications such as fever, infection, severe mucositis, extravasations of chemotherapy, etc., which avoids delaying re-induction/intensification phase. However, when it was administered, patients received 6-mercaptopurine (6-MP) daily and methotrexate (MTX) once weekly.

**Radiotherapy:**

Prophylactic radiotherapy (RT) was rarely administered and only recommended to high risk patients who exhibited T-cell ALL, who were >10 years of age, and who had WBC counts at presentations of > 50 X 109/L. In general, RT was recommended after a period of systemic chemotherapy, normally after six to eight months.

Therapeutic RT was rarely administered, and only for those who were CNS3 on initial diagnosis. Initially, these cases were treated with triple intrathecal therapy (TIT) (cytarabine (ara-C), methotrexate, and hydrocortisone), during induction (phase I) twice weekly injections, corresponding to a course of 12 injections, and administered again after clearance of CSF of blast, through further doses of two more courses of extended TIT. RT was planned to be given later, after 4-6 months, once the patient achieved remission. There were several instances where it was difficult to decide whether to give patients radiotherapy in this university hospital, because of technical delays, such as machines being out of order, or long waiting lists. In these cases patients were transferred to other centers in Cairo to receive RT.

**Additional notes:**

Serious problems were encountered with fungal detection and treatment, because there are no fungal cultures, or galactomannan tests for invasive aspergillosis. The authors depended entirely on clinical suspicion or imaging scans. There is a shortage of antifungal therapy, such as lyophilized amphotericin-B and caspofungin. Usually empiric antifungal therapy was prescribed, using fluconazole or liposomal amphotericin-B (generic brands).

This hospital's infection control teams were only recently initiated; however, the policies and procedures are still not very well established, and in fact they are quite redundant because they are not strictly implemented, nor are they sufficiently resourced, with teams lacking the necessary equipment to do their jobs properly.

Regarding the availability of the antibiotics that are usually available, i.e., the more generic and cheaper brands are readily available, though they may not always be delivered on time or there are significant delays experienced when accurate cultures are needed, which correspond to results that would by necessity require adjustments of the antibiotics.

There are shortages of some types of chemotherapy, including the most common and integral component of maintenance therapy, *i.e*., the 6-MP tablets (always in short supply) and 6-thioguanin (which unfortunately has not been available for years).

L-asparaginase is always in shortage, which obligates the authors to give suboptimal doses to satisfy the needs of all the patients or administer anthracyclines during induction to patients who have the low-risk criteria.

**Table S3 - Treatment outcomes of children with ALL from Egypt and neighboring Middle Eastern countries.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study, year, Country** | **Location, study time, median follow-up** | **Study population, median age (range) years** | **Treatment protocol** | **Death** | **5-year**  **OS, EFS** | **Relapse %** | **Lost to follow up/abandoned treatment** |
| **Our study, 2018,**  **Egypt** | Mansoura University Children Hospital  2011-2016  2.4 years (range: 0.25–5.9 years). | 200 children  Age 5.0 (3.0-8.7) | BFM 90-based | 46 induction deaths (23% of included patients)  21 patients (18.9% of CR patients)  26 patients (63.4% of relapsed patients) | 63.1%, 46% | 20.5%  (41 patients)  RFS: 73.4% | 14 patients (6.5%) |
| **Jastaniah et al.,[6](2015), Saudi Arabia** | Princess Noorah Oncology Center, Jeddah,  2001-2007  6.7 years (range: 0.02–11.67 years). | 224 children  Age 4.9 (1–12.3) | CCG protocols | 35/219 patients (16%).  2.7% induction  3.7% remission  infection (2), toxicity (1), hemorrhagic pancreatitis (1), typhilitis (1), and undocumented (1). | 84.7%, 77% | 15.1% (33 patients)  DFS: 81.4%  Induction failure: 4 (1.9) | ND |
| **Al-Sudiary et al.,[13] (2014), Saudi Arabia** | Various pediatric oncology centers,  2004 to 2008 | 594 children  Age 4.37  (0.1–14.7) | various protocols | 7 patients in induction (5 toxicities, 2 disease progression)  57 patients post-remission | 86.9%, 73.1% | 16% (95 patients)  median of 1.34 years  DFS:79.1% | 32 patients |
| **Tantawy et al.,[14](2013), Egypt** | Ain Shams University, Cairo, Menoufeya University,  2004 – 2005  5 years | 52 children  Age 1-17 | Modified CCG protocol | 6 patients (11.5%)  sepsis was most common cause of death in induction, relapse, (Other: hepatic encephalopathy, CNS thrombosis) | 85%, 73% | 11.5% (6 patients) | ND |
| **Halalsheh et al.,[15]**  **(2011), Jordan** | King Hussein Cancer Center, Amman,  2003 -2009  34.5 months (range: 0.32–84.5) | 300 children  Age 5 (1.0–18.0) | KHCC ALL1102 protocol (based on St. Jude Total XIII and Total XV) | 4 induction deaths  3/4 sepsis  6 non-relapse-related deaths in CR1  (4/6 sepsis) | 89%, 80% | 9% (27 patients)  median 22 months (range 6.7–57.8) after CR | 0 patients |
| **Hussein et al.,[16](2004), Egypt** | National Cancer Institute, Cairo  1998-2000  43 months | 154 children Age < 18 | modified St. Jude Children’s Research Hospital total XIII for high risk ALL | 9 patients (5.8%) induction deaths,  4 (2.6%) refractory leukemia,  7 patients (4.5%) CR  (3 septicemia and 4 methotrexate toxicity) | 65.2%, 75.3% | 17.5% (27 patients) | ND |
| **Dabbous et al.,[17](2003), Lebanon** | American University  of Beirut Medical Center  1990 -1999  5.3 years | 86 children  Age < 1 3 | modified ALGB, the Sallan protocol,  the St. Jude total XIII protocol | 28 patients (34%)  93% of deaths secondary to 1ry disease.  7% in CR | ND | ND | ND |

ND, no data; CR, complete remission; CCG, Children’s Cancer Group; BFM, Berlin-Frankfurt-Münster; OS, overall survival; RFS, relapse-free survival; DFS, disease-free survival; KHCC, King Hussein Cancer Center.

**Figure S1 - Five-year OS outcome according to relapse status.**

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OS, Overall survival.

**Figure S2 - Five-year OS outcome according to time of relapse.**

E:\ACCEPTEDPAPERS\fwdyourmanuscriptjped_2018_540_r1hasbeenaccepted\Fig 3 Survival by Relapse time (Supplement).tif