Clinical characteristics, biologic features and outcome for young adult patients with acute lymphoblastic leukaemia

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Summary

Young adult patients with acute lymphoblastic leukaemia (ALL) represent a unique epidemiologic subgroup in that therapy may be provided by either adult or paediatric oncologists. There seem to be no differences in presenting clinical features, immunophenotypic characteristics, or cytogenetic abnormalities for young adult ALL patients treated on paediatric or adult protocols with the exception of median age (16-paediatric trials versus 19-adult trials). There is no evidence to suggest that age within the 16–21 year old subgroup has any prognostic significance. Compared with patients 1–9 years, young adult ALL patients have a lower incidence of favourable cytogenetics t(12; 21) hyperdiploidy, a slightly increased incidence of the t(9; 22), and an increased frequency of T cell immunophenotype. Compared with patients >30 years, young adult ALL patients have a significantly lower incidence of the t(9; 22). In multiple studies, there is a consistent, large event-free survival and survival advantage for young adult patients treated on paediatric versus adult protocols.

Keywords: acute lymphoblastic leukaemia, young adults, avascular necrosis.

It is well recognized that adult patients with Acute Lymphoblastic Leukaemia (ALL) have a significantly worse outcome compared with children with ALL. As age increases, the percentage of patients having the t(9; 22) or Philadelphia chromosome rises dramatically. Philadelphia chromosome positive (Ph+) ALL is associated with a poor prognosis. Older individuals may have significant co-morbidities that potentially limit the ability to provide intensive therapy. Many adult oncologists report significantly greater toxicity associated with the use of vincristine (VCR) and L-asparaginase (L-ASP) in older patients as compared with younger patients. For this reason, among others, adult ALL protocols feature high dose intermittent chemotherapy with myelosuppressive drugs while paediatric protocols generally feature continuous chemotherapy with intensive use of VCR, L-ASP and steroids.

Young adult patients between 15 and 21 years of age (YA) with ALL represent a unique epidemiologic group in that they may be treated by either adult or paediatric oncologists. Some children’s hospitals have an upper age limit for admission that precludes YA patients from receiving therapy at these facilities.

In the USA, many YA patients continue to receive their primary care from a paediatrician. Paediatricians generally refer YA cancer patients to university-based paediatric oncologists affiliated with large cancer research groups while internists refer YA cancer patients to either community-based or university-based adult oncologists who may or may not be affiliated with a cancer research group. In the USA, more than 85% of patients aged 1–14 years with a diagnosis of cancer are enrolled on a National Cancer Institute (NCI) trial. In contrast, very few YA cancer patients are enrolled on NCI-sponsored clinical trials. In England and Wales, between 1984 and 1994, 80% of patients <14 years of age with a diagnosis of ALL were entered on a clinical trial compared with only 36% for patients 15–29 years of age (Stiller et al, 1999).

Data on biologic and clinical features of ALL, event-free (EFS) and overall survival (OS) and prognostic factors are often derived from large clinical trials. Since YA patients with ALL may be treated on either adult or paediatric clinical trials and the rate of accrual of YA patients to ALL protocols is much lower than that for younger children, the numbers of adolescents with ALL accrued to a particular clinical trial is likely to be low. Excluding infants, YA patients with ALL represent the smallest subgroup of patients entered on both paediatric and adult clinical trials. The low number of YA patients with ALL accrued to clinical trials makes it difficult to make accurate estimates for EFS and OS in this patient population.

Nachman et al (1993) examined the outcome of YA patients entered on the Children’s Cancer Group (CCG) ALL trials between 1983 and 1989. The 6 year EFS for YA patients with ALL was 59%. Chessells et al (1998) examined the influence of age on outcome for paediatric and adult patients with ALL treated on the UKALL X and XA trials. Between 1985 and 1992, the 5-year disease-free survival for patients 15–19 years of age was 35%.

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Recently, the CCG and the Cancer and Leukaemia Group B (CALGB) performed an analysis concerning patients aged 16–21 years at diagnosis with ALL accrued to clinical trials between 1988 and 1998 (CALGB) or 1989–95 (CCG) (Stock et al., 2000). The presenting features for the two patient groups showed similar incidences of white blood cell (WBC) count >50 × 10^9/l, T-cell immunophenotype, and the t(9; 22). There was a large EFS and OS advantage for the YA patients treated on the CCG protocols. Recently, certain European countries (France, the Netherlands, Italy), have also compared outcome for YA patients with ALL treated on either adult or paediatric clinical trials (Boissel et al., 2003; De Bont et al., 2003; Testi et al., 2004). In these studies, as in the CCG/CALGB comparison, YA patients treated on paediatric protocols had a large EFS and OS advantage.

There is now an intense focus on the underserved population of adolescents with cancer. To provide a framework for collaboration between paediatric and adult oncologists in treating YA patients with ALL, it is crucial to review the biologic and clinical characteristics, current treatment outcomes and treatment related toxicities for this subgroup of patients.

Clinical, biological and epidemiologic characteristics of YA patients with ALL

Between 1996 and 2002, YA patients were entered on the CCG 1961 High Risk ALL Trial. Utilizing the data from this clinical trial, and from other 1900 series ALL protocols, we compared presenting features for patients aged 1–9 years, 10–15 years, and 16–21 years at diagnosis. A chi square test for proportions was utilized. The incidence of T-cell ALL was 12.8% in the 1–9 year group, 24.2% in the 10–15 year group and 23.2% in the 16+ year group (P = 0.0005) (H.N. Sather, personal communication). Since T-cell ALL is associated with higher WBC count, lymphomatous features, and higher haemoglobin levels compared with B lineage ALL, we performed separate age group comparisons of presenting features for B lineage and T lineage patients.

Table I shows the presenting features for patients with B precursor ALL entered on the Children’s Oncology Group (COG) 1900 series ALL trials. Older patients had a significantly higher incidence of common ALL antigen negativity, and significantly higher haemoglobin levels compared with younger patients. Older patients had a significantly lower incidence of lymphomatous features (enlarged liver, spleen and/or lymph nodes) compared with younger patients. Interestingly, there was no difference in presenting WBC count between older and younger patients.

Table II shows presenting features for patients with T lineage ALL. As seen for patients with B lineage ALL, older patients with T lineage ALL had significantly higher haemoglobin levels and a significantly lower incidence of hepatomegaly and splenomegaly compared with younger patients.

The Medical Research Council (MRC) data showed a higher incidence of t(9; 22) with increasing age (Chessells et al., 1998). The t(9;22) was seen in 1–3% of patients aged 1–9 years, 3–4% of patients aged 10–19 and 12.2% of patients aged 20–24 years. On the CCG 1961 trial, 7.5% of patients aged 16–21 years with evaluable cytogenetics demonstrated a t(9;22) (Nachman et al., 2004). Patients ≥10 years of age with B precursor ALL have a significantly lower rate of the t(12; 21) translocation and a lower incidence of high hyperdiploidy compared with younger patients (Chessells et al., 1997; Plasschaert et al., 2004).

Drug sensitivity testing revealed that leukaemic cells from older patients demonstrated an increased in vitro drug resistance to prednisone and daunomycin (DNR) (Pieters et al., 1998).

While there are major differences in presenting features for patients aged 1–9 years versus those aged 10–21 years, there

| Table I. Incidence of presenting features by age B-lineage ALL. |
|---------------------------------|----------------|----------------|----------------|----------------|
|                                | 1–9 years (%) | 10–15 years (%) | 16+ years (%) | P-value |
| WBC count >50 × 10^9/l          | 67.7          | 67.7           | 65.8          | 0.50    |
| Common ALL antigen negative     | 4.2           | 8.4            | 8.4           | 0.0001  |
| Normal liver                    | 46.3          | 60.1           | 69.4          | 0.0000  |
| Normal spleen                   | 49            | 54.2           | 58.8          | 0.05    |
| Normal nodes                    | 48.5          | 56.3           | 61.7          | 0.0007  |
| Haemoglobin >11 g               | 8.2           | 22.4           | 27.3          | 0.0000  |

| Table II. Incidence of presenting features by age T-lineage ALL. |
|---------------------------------|----------------|----------------|----------------|----------------|
|                                | 1–9 years (%) | 10–15 years (%) | 16+ years (%) | P-value |
| WBC count >50 × 10^9/l          | 62.4          | 50.3           | 60             | 0.3     |
| Common ALL antigen negative     | 69.1          | 75             | 73.8           | 0.038   |
| Normal liver                    | 37.3          | 48.8           | 48.5           | 0.06    |
| Normal spleen                   | 29.4          | 44.5           | 40.0           | 0.002   |
| Normal nodes                    | 24.4          | 33.7           | 31.1           | 0.13    |
| Haemoglobin >11 g               | 31.1          | 51.0           | 60.5           | 0.0003  |
appears to be no significant difference in presenting features for patients 10–15 years of age and those 16–21 years of age, with the exception that, in the CCG 1961 trial, the percentage of Hispanic patients decreased and the percentage of African American patients increased in the 16–21 year group compared with the 10–15 year group.

**Treatment**

There are major differences in chemotherapy between paediatric and adult ALL protocols. The majority of paediatric ALL protocols are based on a model developed in Germany by Dr Rhiem, the so-called ‘Berlin–Frankfurt–Münster’ (BFM) protocol. BFM-type therapy is based on the Goldie–COLDman hypothesis, which suggests that early chemotherapy intensification is essential for cure in ALL and the Norton–Simon hypothesis which suggests that a late intensification with new drugs or analogs of previously used drugs is necessary to eliminate drug-resistant cells surviving initial chemotherapy. The CCG-modified BFM therapy is shown in Table III. A four-drug induction including VCR, perndisolone (PDN), l-ASP and DNR is followed by an intensive consolidation phase including two courses of cytoxan (CTX), cytosine arabinoside (ARA-C) and six mercaptopurine (6MP), in conjunction with intensive intrathecal methotrexate (MTX) with or without cranial radiation. In the original BFM protocol, a short interim maintenance phase consisting of daily oral 6MP and weekly oral MTX was given. In more recent iterations of the protocol, European investigations have utilized high dose MTX with leucovorin rescue during this phase. For some patients, American investigators have administered the so-called ‘Capizzi’ MTX regimen: VCR on day 1, i.v. MTX without rescue on day 1 and l-ASP on day 2 with courses repeated at 10-day intervals during interim maintenance. Following interim maintenance, patients receive a delayed reinduction-reconsolidation phase (European-protocol II: American-de- layed intensification). During this phase, dexamethasone (DXM) replaces PDN, doxorubicin (DOX) replaces DNR, and six thioguanine (6TG) replaces 6MP. Patients then receive maintenance therapy consisting of daily oral 6MP and weekly oral MTX. In certain protocols, patients also receive monthly pulses of VCR and either PDN or DXM. Thus, paediatric protocols are characterized by dose intensive use of non-myelosuppressive drugs, such as VCR, l-ASP, and steroids, and a continuous antimetabolite-based maintenance.

A significant fraction of ALL patients >40 years of age have the so-called t(9; 22). Ph+ positive ALL has a poor outcome utilizing typical ‘paediatric’ protocols. There is also perception on the part of adult oncologists that older individuals have significantly more toxicity associated with VCR and l-ASP compared with younger individuals. Therefore, most adult protocols incorporate blocks of high dose intermittent myelosuppressive chemotherapy including anthracyclines, CTX, etoposide (VP-16), and high doses of ARA-C (Linker et al, 2002; Kantarjian et al, 2004). Few adult protocols incorporate a delayed intensification phase and duration of therapy is generally shorter compared with paediatric protocols.

Within the past 5 years a number of groups have compared the outcome for YA patients treated on either paediatric or adult cooperative group trials. In the first published experience, the CCG and CALGB compared outcome for young adult patients 16–21 years of age treated between 1988 and 1998 (CALGB) or 1989–95 (CCG) (Stock et al, 2000). CALGB trials utilized the hyper-CVAD regimen (Kantarjian et al, 2004) consisting of eight cycles of chemotherapy with courses of fractionated CTX, DNR, VCR and DXM, alternating with courses of continuous infusion moderate dose MTX plus high dose ARA-C (see Table IV). This was followed by 2 years of maintenance therapy with VCR, PDN, 6MP and MTX.

The majority of YA patients treated on CCG protocols received either CCG-modified BFM or augmented BFM.

### Table III. CCG-modified BFM therapy (CM-BFM).

<table>
<thead>
<tr>
<th>Phase</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>PRED 60 mg/m² p.o. d 1–28 (b.i.d. or t.i.d.) then taper</td>
</tr>
<tr>
<td></td>
<td>VCR 1·5 mg/m² i.v. d 1, 8, 15 and 22</td>
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<tr>
<td></td>
<td>DNR 25 mg/m² i.v. d 1, 8, 15 and 22</td>
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<tr>
<td></td>
<td>t-ASP 6000 U/m² i.m. three times per week × 3 weeks beginning d 3</td>
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<tr>
<td></td>
<td>IT ARA-C d 1 (age-adjusted dose)</td>
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<td></td>
<td>IT MTX d 8 (age-adjusted dose)</td>
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<tr>
<td>Consolidation</td>
<td>PRED Taper</td>
</tr>
<tr>
<td></td>
<td>CPM 1000 mg/m² i.v. d 0, 14</td>
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<td></td>
<td>6-MP 60 mg/m² p.o. d 0–27</td>
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<tr>
<td></td>
<td>ARA-C 75 mg/m² i.v. d 1–4, 8–11, 15–18, 22–25</td>
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<tr>
<td></td>
<td>IT MTX d 1, 8, 15, 22</td>
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<tr>
<td></td>
<td>RT 1800 cGy cranial for no CNS disease at diagnosis</td>
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<tr>
<td></td>
<td>2400 cGy cranial + 600 cGy spinal for CNS disease at diagnosis</td>
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<tr>
<td>Interim maintenance (8 weeks)</td>
<td>6-MP 60 mg/m² q.d. p.o. d 0–41</td>
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<tr>
<td></td>
<td>MTX 15 mg/m² q.w. p.o. d 0, 7, 14, 21, 28, 35</td>
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<tr>
<td>Delayed intensification (7 weeks)</td>
<td>Reinduction (4 weeks)</td>
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<tr>
<td></td>
<td>DEX 10 mg/m² p.o. q.d. d 0–20, then taper for 7 d</td>
</tr>
<tr>
<td></td>
<td>VCR 1·5 mg/m² i.v. d 0, 7, 14</td>
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<tr>
<td></td>
<td>DOX 25 mg/m² i.v. d 0, 7, 14</td>
</tr>
<tr>
<td></td>
<td>t-ASP 600 U/m² i.m. ds 3, 5, 7, 10, 12, 14</td>
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<tr>
<td>Reconsolidation (3 weeks)</td>
<td>CPM 1000 mg/m² i.v. d 28</td>
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<tr>
<td></td>
<td>6-TG 60 mg/m² p.o. q.d. d 28–41</td>
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<tr>
<td></td>
<td>ARA-C 75 mg/m² subq/i.v. d 29–32, 36–39</td>
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<tr>
<td>Maintenance (12-week cycles)</td>
<td>IT MTX d 29, 36</td>
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<tr>
<td></td>
<td>VCR 1·5 mg/m² i.v. d 0, 28, 56</td>
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<tr>
<td></td>
<td>PRED 60 mg/m² p.o. q.d. d 0–4, 28–32, 56–60</td>
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<td>6-MP 75 mg/m² p.o. d 0–83</td>
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<td></td>
<td>MTX 20 mg/m² p.o. d 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77</td>
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<td></td>
<td>IT MTX d 0</td>
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</table>

CNS, central nervous system.
Table IV. Hyper CVAD regimen.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>1, 3, 5, 7*</td>
<td>Cyclophosphamide 300 mg/m² i.v. q 12 h x 6 doses d 1–3, Vinristine 2 mg i.v. d 4, 11, Doxorubicin 50 mg/m² i.v. d 4, Dexamethasone 40 mg/d p.o. d 1–4 and d 11–14, IT Methotrexate 12 mg on d 2†, IT ARA-C 100 mg on d 8†</td>
</tr>
<tr>
<td>2, 4, 6, 8*</td>
<td>Methotrexate 200 mg/m² i.v. over 2 h d 1, Methotrexate 800 mg/m² i.v. over 22 h d 1, ARA-C 3 g/m² over 2 h q 12 h x 4 doses, d 2, 3, IT Methotrexate 12 mg on d 2†, IT ARA-C 100 mg on d 8†</td>
</tr>
<tr>
<td>Maintenance (to 2 years)</td>
<td>Vincristine 2.0 mg i.v. d 1, 6MP 50 mg p.o. i.d. d 1–28, Methotrexate 20 mg/m² d 1, 8, 15, 22, Prednisone 200 mg p.o. d 1–5</td>
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*Courses given following recovery of WBC count >30 x 10⁹/l and platelet >60 x 10⁹/L.
†High risk for central nervous system (CNS) disease – cycles 1–8; low risk cycles 1, 2: unknown risk cycle 1–4.

Compared with CCG-modified BFM, patients receiving augmented BFM received additional courses of VCR and l-ASP during initial consolidation and delayed intensification phases. ‘Capizzi’ MTX was administered during interim maintenance phases. The MTX dose was escalated with each course; no leucovorin rescue was given. Patients received a second interim maintenance and delayed intensification phase prior to beginning maintenance. The augmented BFM chemotherapy regimen is shown in Table V. A comparison of dose intensity for various drugs in CCG-modified BFM, augmented BFM and Hyper-CVAD is shown in Table VI.

Comparing YA patients treated on CALGB and CCG protocols, patients treated on CCG protocols received significantly more VCR, steroid, and l-ASP and significantly less CTX and ARA-C compared with patients treated on the CALGB protocols. Patients in both groups were well matched for major presenting features such as WBC count, unfavourable cytogenetic features, and immunophenotype. For patients treated on CALGB trials, the induction rate was 93% and the 6-year EFS was 38%. For patients treated on CCG trials, the induction rate was 96% and the 6-year EFS was 63%.

In a similar study design, French investigators compared outcomes for patients 15–20 years of age treated on either the French Acute Lymphoblastic Leukaemia Group (FRALLE) paediatric trial (n = 77) or the adult Leucémies Aiguës Lymphoblastiques de l’Adulte (LALA) trial (n = 100) between June 1993 and November 1999 (Boissel et al, 2003). FRALLE chemotherapy included a prednisone prophase followed by a four-drug induction including VCR, PDN, DNR, and l-ASP. Consolidation included ARA-C, VP-16, 6TG followed by VCR, PDN, oral 6MP and oral MTX. Delayed intensification consisted of a 4-drug reinduction, of vindesine, ADR, DXM and l-ASP followed by reconsolidation. After a brief interim maintenance (VCR, PDN, oral 6-MP, oral MTX) that included 18 Gy cranial radiotherapy, patients received a second delayed intensification followed by maintenance therapy with the same

Table V. Augmented BFM therapy (A-BFM).

<table>
<thead>
<tr>
<th>Induction</th>
<th>VCR 1·5 mg/m² i.v. d 1, 8, 15 and 22</th>
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<tbody>
<tr>
<td>PRED 60 mg/m² p.o. d 1–28 (b.i.d or t.i.d.) then taper</td>
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<tr>
<td>DNR 25 mg/m² i.v. d 1, 8, 15 and 22</td>
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<tr>
<td>l-ASP 6000 U/m² i.m. three times per week x 3 weeks beginning on d 3</td>
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<tr>
<td>IT ARA-C d 1 (age-adjusted dose)</td>
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<td>IT MTX d 8 (age-adjusted dose)</td>
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Consolidation (9 weeks)

| CPM 1000 mg/m² i.v. d 0, 28 |
| ARA-C 75 mg/m² subq/i.v. d 1–4, 8–11, 29–32, 36–39 |
| 6-MP 60 mg/m² p.o. d 0–13, 28–41 |
| VCR 1·5 mg/m² i.v. d 14, 21, 42, 49 |
| l-ASP 6000 U/m² i.m. d 14, 16, 18, 21, 23, 25, 42, 44, 46, 49, 51, 53 |
| IT MTX d 1, 8, 15, 22 |
| RT 1800 cGy cranial, for no CNS disease at diagnosis; 2400 cranial + 600 cGy + spinal for CNS disease |

Interim maintenance I (8 weeks)

| VCR 1·5 mg/m² i.v. d 0, 10, 20, 30, 40 |
| MTX 100 mg/m² i.v. d 0, 10, 20, 30, 40 (escalate by 50 mg/m²/dose) |
| l-ASP 15 000 U/m² i.m. d 1, 11, 21, 31, 41 |

Delayed intensification I (8 weeks)

| Reinduction (4 weeks) | DEX 10 mg/m² p.o. q.d. d 0–20, then taper for 7 d |
| VCR 1·5 mg/m² i.v. d 0, 14, 21 |
| DOX 25 mg/m² i.v. d 0, 7, 14 |
| l-ASP 600 U/m² i.m. d 3, 5, 7, 10, 12, 14 |

Reconsolidation (4 weeks)

| CPM 1000 mg/m² i.v. d 28 |
| 6-TG 60 mg/m² p.o. d 28–41 |
| ARA-C 75 mg/m² s.c./i.v. d 29–32, 36–39 |
| IT MTX d 29, 36 |
| VCR 1·5 mg/m² i.v. d 42, 49 |
| l-ASP 6000 U/m² i.m. d 42, 44, 46, 51, 53 |

Interim maintenance II See interim maintenance I except additional IT MTX on d 0, 20, 40

Delayed intensification II See delayed intensification I

Maintenance (12-week cycles)

| VCR 1·5 mg/m² i.v. d 0, 28, 56 |
| PRED 60 mg/m² p.o. q.d. d 0–4, 28–32, 56–60 |
| 6-MP 75 mg/m² p.o. q.d. d 0–83 |
| MTX 20 mg/m² p.o. d 7, 14, 21, 28, 35, 42, 56, 63, 70, 77 |
| IT MTX d 0 |

PDN, oral 6MP and oral MTX. Delayed intensification consisted of a 4-drug reinduction, of vindesine, ADR, DXM and l-ASP followed by reconsolidation. After a brief interim maintenance (VCR, PDN, oral 6-MP, oral MTX) that included 18 Gy cranial radiotherapy, patients received a second delayed intensification followed by maintenance therapy with the same
and the FRALLE trials received significantly more VCR, steroid, and cranial radiation.

The FRALLE 93 trial, unfavourable features included WBC count if a matched sibling was available, or an autograft. For the protocol. On both trials, patients with unfavourable prognostic

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The incidence of steroid/l-ASP-induced diabetes and pancreatitis increased with age.

The CCG 1882 study was the first CCG study in which every patient received either CCG-modified BFM or augmented BFM chemotherapy. CCG 1882 was also the first study to include patients >10 years of age and WBC count <5×10^9/l in the high risk group. During the course of the 1882 study, avascular necrosis of bone (AVN) was identified as a significant cause of morbidity for patients >10 years of age (Mattano et al., 2000).

On the CCG 1882 study, 14.2% of patients >10 years of age developed AVN compared with a 1% incidence for patients <10 years of age. In patients >10 years, the incidence was higher for females than for males, 17.4% vs. 11.7% (P = 0.03). The incidence in YA patients 16–21 years of age was 18%.

Patients on CCG 1882 were assigned to a rapid or slow response group based on day 7 marrow morphology. RERs (day 7 M1/M2 marrow) received CCG-modified BFM with or without cranial radiation. SERs (day 7 M3 marrow) were randomized to receive CCG-modified BFM with cranial radiation or augmented BFM with cranial radiation therapy. Patients receiving CCG-modified BFM received one DI Phase while patients receiving augmented BFM received two DI phases. Each DI Phase included DXM 10 mg/m^2 on day 1–21. The incidence of AVN was 8% for RER patients, 15% for SER patients receiving one DI phase and 23% for SER patients receiving two DI phases. It is unclear why SER patients receiving one DI phase had a twofold increased risk of AVN compared with RER patients receiving the same therapy.

Since continuous steroid exposure was thought to be associated with an increased risk for AVN, on the CCG 1961 protocol, RER patients randomized to two DI phases and all SER patients (two DI phases) received DXM (10 mg/m^2/d) on day 1–7 and 15–21 of each DI phase. RER patients randomized to one DI phase received continuous DXM (10 mg/m^2/d) on day 1–21. For patients >10 years, RER patients receiving one DI (continuous DEX) had an AVN incidence of 13.4% compared with 7.5% for patients receiving two DI phases (discontinuous DXM) (P = 0.002) (Mattano et al., 2003). For patients receiving the augmented intensity regimens, the incidence of AVN was 15.2% for patients receiving continuous DXM vs. 5.3% for those receiving discontinuous DXM. In the YA subgroup, the incidence of AVN was 28% for patients receiving discontinuous DXM vs. 12.4% for those receiving continuous DXM.

**Discussion**

Compared with younger patients, YA patients with ALL have a higher incidence of T-cell immunophenotype, higher haemoglobin levels, a higher (although still low) rate of the t(9; 22), a lower incidence of favourable cytogenetics such as high hyperdiploidy or the t(12; 21), and a lower incidence of lymphomatous features.

A recent publication has shown that ALL in older adolescents may have a different pattern of promoter gene methylation, compared with younger patients (Roman-Gomez et al., 2004).

There is little clinical and/or biological difference between patients 10 and 15 years of age and those aged 16–21 years. There seems to be no difference in presenting features for YA patients treated on paediatric or adult protocols with the exception that the median age is 16 for paediatric and 19 for the adult protocols.

In a recent series of publications, the outcome for children aged 1–9 years was consistently better than that for patients aged 10–21 years (Eden et al., 2000; Gaynor et al., 2000; Harms et al., 2000; Kamps et al., 2000; Maloney et al., 2000; Pui et al., 2000; Schrappe et al., 2000; Silverman et al., 2000). However, differences in presenting features, particularly the presence of favourable cytogenetics in the 1–9 age group, were not accounted for. In a recent analysis of the CCG 1961 high risk ALL trial, the small number of YA patients with high hyperdiploidy had an excellent outcome (H.N. Sather, personal communication). At present, the EFS for YA patients treated on paediatric trials is 55–70% and the survival is between 65% and 75%. YA patients have a higher incidence of induction death and death in remission compared with younger patients (Rubnitz et al., 2004).

AVN is a serious treatment complication in YA patients with ALL in paediatric trials. The use of discontinuous DXM in delayed intensification phases produces a significant decrease in the incidence of AVN for YA patients (Mattano et al., 2003).

In multiple comparisons of YA patients with ALL treated on paediatric and adult protocols, there was a consistent and large difference in both EFS and OS, favouring patients treated on paediatric trials with the EFS advantage ranging from 20% to 30%. In the individual comparative studies, presenting clinical and biologic features for the YA patients treated on either paediatric or adult protocols were similar, with the exception of median age. Ph+ ALL occurred in 3–6% of YA patients.

In an editorial accompanying the presentation of the French FRAALLE and LALA comparison, Schiffer (2003) raised the issue as to whether the outcome difference favouring YA patients treated on paediatric protocols was a consequence of better regimens, better doctors, or both.

The most likely explanation for the large EFS and OS difference favouring YA patients with ALL treated on paediatric protocols is the significant differences in chemotherapy regimens utilized by paediatric and adult oncologists, although other factors might be operating as well. In general, paediatric protocols utilize more steroids, VCR and l-ASP compared with adult protocols and lower amounts of alkylating agents, high dose ARA-C, and anthracyclines. Most paediatric protocols utilize a BFM-based model in which an intensive induction consolidation phase is followed by an interim maintenance phase and then a delayed intensification phase. Maintenance therapy generally consists of daily oral 6MP, weekly oral or i.m. MTX ± steroid/VCR pulses. Certain paediatric protocols incorporate a second application of delayed intensification. Since the introduction of a delayed...
intensification phase by the BFM group, paediatric studies attempting to eliminate this phase have uniformly resulted in a significant decrement in both EFS and OS. None of the four adult trials in the comparative studies utilized a delayed intensification phase of therapy.

Because of the poorer general outcome for adult compared with childhood ALL, there is increased utilization of autologous and allogeneic bone marrow transplantation in first remission in adult compared with paediatric protocols. In paediatric protocols, allogeneic transplantation from matched sibling donors in first remission is of proven benefit only in the small subset of patients with t(9;22).

Other issues may also contribute to the superior outcome found for YA patients treated on paediatric protocols. ALL is an uncommon neoplasm for adult oncologists. Compared with paediatric ALL, adult ALL is a more heterogeneous disease. Beyond 25–30 years, the incidence of t(9;22) rapidly increases and comorbid conditions become an increasingly important consideration in treatment design, particularly in elderly individuals. Part of the rationale for the design of adult ALL trials is the perception that older patients have significantly increased toxicity associated with the administration of VCR and l-ASP compared with younger patients. Since YA patients 16–21 years of age represent a very small fraction of patients entered on adult ALL trials, they are lumped together with older patients and treated on a common protocol.

The vast majority of YA patients with ALL treated on paediatric trials are treated by university-based paediatric oncologists while 25–40% of patients treated on adult trials are treated by community-based adult oncologists. However, a UK study suggested no difference in outcome for adults with ALL treated by university or community based adult oncologists (Benjamin et al, 2000), but this issue has not been examined in the USA adult ALL trials.

Physician compliance with drug administration as mandated by protocol may be an important issue. In his editorial (Schiffer, 2003), Dr Schiffer commented on protocol compliance by paediatric oncologists as ‘military precision on the basis of a near religious conviction about the necessity of maintaining prescribed dose and schedule come hell, high water, birthdays, Bastille day, or Christmas’. He concluded that, although there are few if any studies proving an advantage for such rigor, it is likely that neither adult university-based or community-based oncologists meet the paediatric standard. In a recent article, dealing with who should be treating adolescents with ALL, Jeha (2003) argued that adults and paediatric oncologists should utilize common protocols to treat these patients.

Currently, the two largest adult oncology groups in the USA are developing a clinical trial for young adult patients with ALL which will utilize one arm of the current COG AALL0232 high risk ALL protocol. On the AALL0232 trial, standard therapy for YA patients with a rapid morphologic response and <0.1% minimal residual disease on day 28 as measured by flow cytomtery will be ‘hemi-augmented’ BFM-therapy (augmented BFM with only one interim maintenance and one delayed intensification phase) which proved to be the best arm in the CCG 1961 trial for high risk RER patients (Seibel et al, 2003). On CCG 1961, this hemi-augmented BFM had an equivalent outcome to full augmented BFM (two interim maintenance and two DI phases). The AALL0232 trial is evaluating DXM at 10 mg/m\(^2\)/d \(\times 14\) d versus PDN at 60 mg/m\(^2\)/d \(\times 28\) d during induction and high dose MTX with Leucovorin rescue versus Capizzi MTX in the first interim maintenance phase. At present, the adult groups plan to utilize the dexamethasone and Capizzi MTX arm for their trial. ALL patients 15–30 years of age will be eligible for this trial.

As the rate of both bone marrow and extramedullary relapse decreases, induction death and death in remission becomes an increasingly important cause of treatment failure in YA patients with ALL. We may be able to decrease the incidence of induction deaths and deaths in remission by providing better supportive care or by identifying upfront those patients likely to experience severe toxicity with current therapy. Identification of key genetic polymorphisms that influence drug metabolism may play an important role. We must also develop more precise treatment response measures to predict which patients might achieve cure with less aggressive treatment and which patients require either more intensive (bone marrow transplant as a possibility) or novel therapies to improve cure. Determination of minimal residual disease by molecular or flow cytometric tools might be important in this regard. We must also determine whether, utilizing similar, if not identical treatment regimens, adult university-based or community-based oncologists can achieve similar EFS results to those obtained by paediatric oncologists for YA patients with ALL. Answers to these important questions should be forthcoming in the next 5–10 years.

References


