Lessons learnt from 50 years of clinical trials curing childhood acute lymphoblastic leukaemia
(with 10 essential medicines)

Catherine Cole
MBBS W Aust FRACP(Paed) FRCPA(Haem)
COI and disclosures

• COI-None
  – “if you are tempted to eat, drink or travel courtesy of pharma, ask yourself “what would my patients think of this?””

• Disclosure-PBAC
Both adult and pediatric oncologists have made much progress, but for various reasons I suggest that the treatment of children has often led the way. Pediatric oncologists early defined the two essential ingredients of successful cancer management:

- True collaboration from the outset among all disciplines, and
- Recognition that cancer in children involves sensitive tumours with effective methods of control.
Looking forward we see a wide and open road with well spaced way-stops en route to our final destination.

Some of these way-stops surely are the development of ever more refined and precisely targeted methods of treatment, so that increasing numbers of successfully treated children of today do not become the chronically ill adults of tomorrow.

Dan d’Angio
Pediatric Cancer in Perspective: Cure is not enough.
Acute lymphoblastic leukaemia

- 25% of cancer <15 years
  - 19% <20 years
- Leading cause of childhood cancer death

**Figure 1.** Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.
1950s

- Freireich (1948) folate added to leukaemia cell cultures - antifolate-aminopterin
- Hitchens and Elion 6MP - Nobel Prize
1960s-drugs

- Emil (Tom) Frei and Emil (Jay) Freireich NCI
  - Combined drugs to avoid resistance (TB)
  - Prognostic importance of age and initial WCC
  - Empiric antibiotics
  - Non-myelosuppressive vinca alkaloids
  - Allopurinol + urinary alkalinisation

- CDC- *pneumocystis carinii*
  - Pentamadine and cotrimoxazole
1960s-drugs

• Haig Riehm
  – Berlin Frankfurt Munster BFM co-operative group
  – 4 drug induction and 4 drug consolidation

• Don Pinkel SJCRH
  • Total therapy combining all known effective agents to attempt a cure of the disease.
  • “TT consists of rapid and efficient induction of complete remission with prednisone and vincristine in order to minimize early attrition, cranial, or craniospinal irradiation during the first month of complete remission to prevent meningeal relapse, and multiple-drug chemotherapy for 2 to 3 years to eradicate residual systemic leukemia.”
1970s-science

- Cytogenetics
- Immunophenotype-flow
- BFM-reintensification
- Dana Farber-weekly asparaginase
- Intrathecal therapy replaces RT in “good risk” patients
- High dose methotrexate reduces the risk of testicular relapse
- Anthracyclines
- Cox developed multivariate statistical methods to ensure comparable groups in randomised trials
1980s—personalised medicine

- Median survival >10 years
- Poor risk groups
  - Infants
  - Trisomy 21
  - Resistant and relapsing leukaemia balanced against fatal infection
- Adverse host pharmacodynamics and pharmacokinetics
- Variation in treatment adherence (compliance)

Blood Cancer J. Apr 2014; The evolution of clinical trials for infant acute lymphoblastic leukemia
R S Kotecha,
1990s

Late effects of therapy
- long term follow up
- survivor screening

Dexamethasone better than prednisone

Pegylated asparaginase

The drugs used to treat ALL in 1990 had been in use since the sixties with progressive improvement coming from risk directed therapy and better supportive care allowing for treatment to be intensified.

- Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children’s Cancer Group
2000s-more science personalised care

- Depth of response to early therapy
- Minimal Residual Disease
  - PCR Ig/TCR genes/fusion transcripts
  - Flow cytometry aberrant IP
  - Deep sequencing


Michael J. Brisco,* Sue Latham,* Rosemary Sutton,† Elizabeth Hughes,* Vicki Wilczek,* Katrina van Zanten,* Bradley Budgen,* Anita Y. Bahar,† Maria Malec,† Pamela J. Sykes,* Bryone J. Kuss,* Keith Waters,‡ Nicola C. Venn,† Jodie E. Giles,† Michelle Haber,† Murray D. Norris,† Glenn M. Marshall, § and Alexander A. Morley*
• The improvement in outcome in these 5 decades had cemented the paradigm of treatment for all childhood cancers on co-operative group randomised controlled trials in a paediatric hospital.
• This paradigm puts the patient’s need to be cured first and recognises the best chance of cure is the first time the patient is treated.
• This may seem self evident, but it is important because it explains the emphasis on Phase III clinical trials in paediatric cancer centres over phase I and II drug trials.
Clinical trials

Phase III RCT of proposed therapy vs current best therapy

Disease-free patient

De-novo/localised disease

Standard (of) care
Clinical trials

- Relapsed/end-stage disease
- Relapsed/metastatic /high risk disease
- De-novo/localised disease
- Disease-free
- Phase III
- Palliative care QOL
- Patient
Clinical trials

Preclinical/animal models

Phase I

10

Relapsed/end-stage disease

Phase II

100

Relapsed/metastatic /high risk disease

Phase III

De-novo/localised disease

Disease-free

Palliative care QOL

Drug

Patient
Clinical trials

- Preclinical/animal models
  - Phase I (10)
    - Relapsed/end-stage disease
  - Phase II (100)
    - Relapsed/metastatic/high risk disease
  - Phase III (1000)
    - De-novo/localised disease

- Palliative care QOL

- Patient
Clinical trials

Drug

Preclinical/animal models

Phase I

Relapsed/end-stage disease

Phase II

Relapsed/metastatic/high risk disease

Phase III

De-novo/localised disease

Palliative care QOL

(10) patient

(100) drug

(1000) patient

(10000) drug
Clinical trials

- Preclinical/animal models
  - Phase I
    - 10
    - Phase I
    - Phase II
      - 100
      - Phase II
      - Phase III
      - Standard (of) care
        - Disease-free
        - patient
        - Marketing
  - Relapsed/end-stage disease
  - Relapsed/metastatic /high risk disease
  - De-novo/localised disease
  - Palliative care QOL
Preclinical/animal models

Phase I
- Relapsed/end-stage disease

Phase II
- Relapsed/metastatic/high risk disease

Phase III
- De-novo/localised disease
- Disease-free

Palliative care QOL

Marketing

Unmet need

Disease-free

drug

10

100
Drug Clinical trials

- Preclinical/animal models
  - Phase I
    - 10
      - Relapsed/end-stage disease
  - Phase II
    - 100
      - Relapsed/metastatic/high risk disease
  - Phase III
    - De-novo/localised disease
    - Standard (of) care
      - Disease-free
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- Palliative care QOL
Clinical trials

Preclinical/animal models

Phase I

Phase II

Phase III

De-novo/localised disease

Relapsed/metastatic/high risk disease

Relapsed/end-stage disease

Palliative care QOL

Drug

Marketing

Disease-free

Standard (of) care

patient
Fig 1. Emerging themes in the design of oncology randomized clinical trials (RCTs).

**Appeal for better clinical trials and improved reporting (1983)**

1. To ensure that trials have been performed on an adequate number of patients before they are reported and that patients are not inappropriately excluded in determining results.
2. That the meaningless comparisons of survival of responding and nonresponding patients be excluded.
3. That more stringent criteria that relate to true clinical benefit be required as measures of response to treatment.
4. That emphasis be placed on studies which seek to derive valid indices for measurement of quality as well as quantity of patient survival.
5. That equal weight be given to “positive” and “negative” trials.

**Emerging themes in design of oncology RCTs**

- **A. Appropriate design of clinical trials.**
- **B. Clinically relevant endpoints.**
- **C. Reporting of trials and avoidance of bias.**

**Appeal for better clinical trials and improved reporting (2008)**

1. Investigators (and editors) should adhere to guidelines for the design and reporting of clinical trials.
2. Oncologists should reduce their participation in phase II trials; they should be given more academic and other credit for supporting phase III trials with potential to change practice.
3. Surrogate endpoints for survival, including biomarkers in trials of targeted therapy, should only be used if they have been demonstrated to correlate with overall survival.
4. RCTs should include appropriate and validated measures of quality of life and/or symptom control.
5. RCTs should include a pharmacoeconomic analysis to evaluate the cost-benefit of new treatments.
6. Efforts should continue to reduce publication and sponsorship biases.
64% of cancer drug trials in Australia are funded by industry.

Industry was found to predominantly sponsor drug trials involving metastatic disease, where therapeutic gains can be more promptly translated into commercial success.

Randomised phase III trials for de novo disease are often multinational and, because survival is often the endpoint, take many years to achieve a result.
Clinical trials

Preclinical/animal models

Phase I

- Relapsed/end-stage disease

Phase II

- Relapsed/metastatic/high risk disease

Phase III

- Disease-free

- De-novo/localised disease

Palliative care QOL

Patient

10

100

65% (>95%)

1000

Drug
Cost of NCI Pediatric Cancer Clinical Trials Cooperative Group Program

$25 million/year (COG)

350,000 Patient Years of Life Saved (PYLS) among Children on Clinical Trials

$70 per PYLS
Cost of NCI Pediatric Cancer Clinical Trials Cooperative Group Program

$25 million/year (COG)

600,000 Patient Years of Life Saved (PYLS) among all Children with cancer

$40 per PYLS
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<th>Description</th>
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<td>$3000</td>
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1-2% of the total cost of cancer care is in the running of co-operative group clinical trials.
Cost of Childhood Cancer vs. Other Diseases

per Year of Life Saved

Childhood Cancer ........................................ $3,000
Cholesterol Screening for boys at age 10 years ............... $6,500
Thrombolytic Rx for Acute Myocardial Infarct ............... $33,000
Heart transplant ........................................... $104,000
NAT screening blood-product donors for early HIV infection (viremia phase) ......................... $10,000,000
Clinical trials

Preclinical/animal models

Phase I

10

Phase II

100

Relapsed/end-stage disease

Relapsed/metastatic/high risk disease

65%

(95%)

1000

Phase III

De-novo/localised disease

Disease-free

Patient

Palliative care QOL

$+2\%$
Survival and cure trends for European children, adolescents and young adults diagnosed with acute lymphoblastic leukemia from 1982 to 2002.
Survival and cure trends for European children, adolescents and young adults diagnosed with acute lymphoblastic leukemia from 1982 to 2002.
- Ph+ ALL
  - Ponte di Legno
  - Pre-Imatinib

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The New England Journal of Medicine

Figure 2. Estimates of Disease-free and Overall Survival (±SE) in 267 Patients Treated with Transplantation of Bone Marrow from HLA-Matched Related Donors or Chemotherapy Only.

The curves have been adjusted for waiting time to transplantation, so that the zero on the time axis corresponds to the median time from diagnosis to transplantation (six months); patients were assigned to this treatment group in a time-dependent fashion. Five-year estimates are shown. P values are from the Mantel–Cox test. P<0.001 for the comparison of the two treatments with respect to overall survival; P<0.001 for the comparison with respect to disease-free survival.
Ph+ ALL
an adaptive trial

A
AALL0031
cohort 5 versus historic controls

B
AALL0031
cohort 5 chemotherapy versus HSCT
The future

- Favourable genetic features and rapid early response-
  - 5yr EFS 94.2%, OS 98.7%
    - 75mg/M^2 anthracycline and 1g/M^2 cyclophosphamide
    - Maintenance chemotherapy, embedded quality of life and physical functioning
- 20% relapse
  - Many low risk patients relapse
    - (and many high risk patients are over-treated)
  - Cure<50%
  - COG + IntReALL blinatumomab
    - co-operation from industry
    - Paediatric oncologists clearly know how to run clinical trials.
“What is the use if the treatment is only available to 15% of the world’s population?”

Donald Pinkel

Ponte di Legno statement 2004:

Curing childhood acute lymphoblastic leukaemia with 10 essential medicines

- 1. Asparaginase
- 2. Cyclophosphamide
- 3. Cytarabine
- 4. Dactinomycin
- 5. Daunorubicin
- 6. Doxorubicin
- 7. Mercaptopurine
- 8. Methotrexate
- 9. Thioguanine
- 10. Vincristine
“Children have led us to this high plateau. They have shown us that the mountainside, no matter how strewn with obstacles, can be climbed.

They have shown us that cancer, even when disseminated, can be cured.

Paediatricians are by bent and training dissatisfied with anything short of the perfectly healthy child.

We therefore wait for the work of geneticists and immunologists to bear fruit when cancer, like polio, becomes a curiosity largely of historical interest, and the scalpel, the syringe and the cobalt unit take their place in the medical museum alongside the brace and the respirator.”