BLOOD DISEASES IN CHILDREN WITH DOWN’S SYNDROME: OVERVIEW AND UPDATE

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My major interest is leukaemia, but I also want briefly to discuss normal and abnormal blood values in children with Down’s syndrome (DS) and also mention the immunological abnormalities. I’m going to talk about the transient abnormalities of the blood count that are seen in newborn infants with DS and the associated management problems. I will also discuss the risk of leukaemia in children with DS and then the unique clinical features of the two types of acute leukaemia in childhood in respect of children with DS – lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML).

BLOOD COUNTS

It is important to address the issue of whether children with DS have the same blood counts as children without DS. A fairly recent paper from Paediatric Haematology and Oncology compared 50 children with DS in the post neonatal period with age matched controls. The children with DS had significantly higher mean corpuscular volume (MCV) and haemoglobin, but the levels of all the haematinics – iron, folate etc. were normal. It is not known why children with DS have raised MCV, but of course there are three chromosomes 21 and it may be related to altered folate methylation involving the genes on chromosome 21. From a practical point of view this may cause confusion because these children may get iron deficiency and it must be remembered that their ‘baseline’ MCV may be not the same as everybody else’s.

Looking prospectively at children in the first year of life, a Scandinavian group examined 25 infants serially and a large proportion (64%) was polycythemic in the first two months. Surprisingly, there was no significant difference in the haematocrit between the children with and without congenital heart disease. By 9–12 months the raised MCV and MCH levels were already apparent, but erythropoetin and haematinic levels were normal (Table 1). So, there are a number of studies that confirm there is macrocytosis in children with DS, and this needs to be considered when investigating whether a baby is anaemic and the cause of the anaemia. Obviously the white cell
counts are of interest, particularly in the context of leukaemia, and in fact they are within the normal range during the first year of life. Fascinatingly, the platelet count is raised and there is no real explanation for this. This is very interesting because very often when children with DS get acute myeloid leukaemia it seems to be a leukaemia of platelet precursors – a megakaryocytic leukaemia. Therefore, it can be seen that there are differences in the blood count between children with DS and others and this is very relevant when interpreting the results of laboratory investigations.

IMMUNOLOGICAL ABNORMALITIES

The susceptibility to infection of children with DS is something that causes a lot of problems especially when they are going through treatment for leukaemia. Children with DS also have more problems with autoimmune disease. There have been a number of studies of the immunology of DS but most are not very satisfactory. While crude measurement of the immunoglobins may be normal there are differences and deficiencies in some of the immunoglobulin sub-classes. Levels of IgG₁ and IgG₃ are normal in most studies and IgG₄ and IgG₂ are reduced. To what extent this bears on the increased susceptibility to infection is unclear.

LEUKAEMIA AND LEUKAEMIA-LIKE DISORDERS

The issue of leukaemia and leukaemia-like disorders in children with DS is very interesting not the least because it illustrates the dramatic change in the perception of the families, the paediatricians, and the carers in what is appropriate and what standards of treatment they require. Twenty or thirty years ago, when admittedly the results of treatment for all children with leukaemia weren’t very good, one was often asked to support a policy that everybody felt was right – that these children shouldn’t be treated intensively. Now, of course, they are being treated and many are doing well. There are three types of problem in children with DS:

- The transient abnormality of the blood count in the neonatal period which causes a lot of diagnostic and management problems (so called transient abnormal myelopoiesis; TAM)
- AML, which is very rare in children – about 60–70 new cases/annum in children aged 0–15 years in the UK
- ALL, which is the commonest type of childhood leukaemia: 300–400 new cases/annum overall in children aged 0–15 years in the UK.
Transient abnormal myelopoiesis
To illustrate the problem of TAM in childhood it may be helpful to discuss two case scenarios. The most common one is that I receive a telephone call from a neonatologist to say that they have a baby with DS who has had a blood count while in the special care unit. Although the actual blood count values are normal there are a lot of odd blast cells on the film and everybody is very concerned. When the blood film comes to us for review there are blast cells on it, but otherwise the baby is completely well. No intervention is needed and things soon settle down.

The more unusual situation is illustrated by a little boy born at 37 weeks gestation with DS, a massive septal defect and a very high leukocyte count – 471x10⁹ /l instead of say 10-20x 10⁹ /l as in the average newborn. Many of these were blast cells that were indistinguishable from the blast cells of acute leukaemia. This child was very unstable, there were problems with hydration and ventilation and we were worried that the raised blood count was going to cause sludging and thrombotic problems, so we felt we ought to intervene. We gave some cytotoxic treatment with a minuscule dose of cytarabine and the count got slowly better. His cardiac defect was repaired and he’s been well ever since with no sign of acute leukaemia.

In TAM there are blasts in the blood and blasts in the bone marrow – which in any other circumstances would be diagnostic of acute leukaemia. The blast cells are very unusual immunologically and morphologically – they look like megakaryoblasts, which is an exceptionally rare type of myeloid leukaemia involving the platelet precursors. The blasts in TAM are indistinguishable from those seen in acute leukaemia, but we know that in the newborn as opposed to older children this is a very different situation. In the vast majority of neonates there will be spontaneous improvement of the count. It is very rarely necessary to intervene as in the child I just described.

If you did a routine blood count on all newborn babies with DS how often would you find evidence of TAM? We have considered investigating this ourselves, but there is an ethical issue – the reason for doing this must be explained to the parents and then a decision must be made as to what is done in terms of follow-up if an unusual count is found. We have not yet moved further on this one. My colleague, Prof. Alvin Zipursky, who has a great interest in this problem in an area around Toronto, Canada, has been trying to do this for some years. He feels that blood count abnormalities with evidence of TAM occur in up to about 10% of newborn babies with DS. Very occasionally babies with DS can die in utero from hydrops or can subsequently have
major problems with liver fibrosis in the perinatal period and may die – but this is very rare.

Can TAM occur in normal infants? I think it can – exceptionally rarely, and of course it is difficult to be sure that the child is not a DS mosaic, but nearly always when it occurs, it occurs in DS.

**TAM and AML**

In TAM the morphology, the appearance of the bone marrow and the blood, is indistinguishable from acute leukaemia. One of the recent landmark discoveries in acute leukaemia is that the diseases are associated, not only with genetic changes that serve to drive the leukaemia, but also with cytogenetic changes. These cytogenetic changes can be seen under the microscope, or more recently using fluorescent in situ hybridisation (FISH) which is an elegant method of painting the chromosomes. Clonal cytogenetic abnormalities can occur in children with DS and TAM just as they occur in any type of leukaemia – and yet get better without any treatment. It is known from the follow-up of many neonates with TAM that, apart from those who die in utero from hydrops or who get fibrosis in the liver, the majority get better and remain well. We’re not quite sure why fibrosis of the liver occasionally develops, it may be that the platelet derived growth factor that is produced by the megakaryoblast drives it. That is a very difficult problem to manage and we have lost one or two infants from it. Thus in summary a very small proportion of children with TAM die from complications early in life and probably about 20–25% of children subsequently develop acute myeloid leukaemia which does not resolve spontaneously and the child will die if not treated.

So what do I say to the family of this baby we treated in the neonatal period? When patients like this are referred we are quite frank. We explain that for reasons that are not understood the baby has developed a leukaemia-like disorder – that the transient abnormality gets better, but that there is a risk that the child will subsequently develop myeloid leukaemia. We stress that it is only a small risk and that it would be dangerous and inappropriate to give chemotherapy in the newborn period to try and stop leukaemia developing later. We explain that if the child does develop leukaemia later it is a very treatable and curable condition and if it’s going to happen it will happen within the first two years or so of life. That is the difficult part, since it means that the parents are sitting over a precipice, but it would obviously be wrong to withhold this information.
TAM: Unresolved issues

So what are the unresolved issues about transient abnormal myelopoiesis?

- How many infants have it and what predisposes to it?
  
  There has been a suggestion that it partly depends on which parent has contributed the extra chromosome 21, but, as far as I’m aware, that hasn’t been followed up and supported.

- What is the real risk of subsequent AML?
  
  It is thought to be about 20%.

- Do all children who get AML later always have preceding TAM?

- Children with DS also have an increased risk of lymphoblastic leukaemia. Does TAM predispose to lymphoblastic leukaemia?

In summary, TAM, this unique disorder in the newborn infant, virtually confined to DS, has, in general, a very good prognosis and we don’t know why. The less treatment the patients can be given the better. If forced to give treatment you may want to gradually reduce the blood count steadily with a little bit with low doses of cytotoxic drugs such as cytarabine, but this is very rarely necessary.

Leukaemia after the neonatal period

We’ve known for many years that there is an increased risk of acute leukaemia in children with DS. One of the earliest reports was in 1930\(^3\) and Dr Krivit, who is still medically active at the age of almost 80, wrote one of the first papers on this.\(^4\) There was a lot of confusion, which can be seen from the early literature, regarding whether the children were at increased risk of myeloid leukaemia or lymphoblastic leukaemia or both.\(^5,6\) Now we know that the confusion in those earlier series was because the methods available then were not good enough to classify the leukaemia, it was a case of looking under the microscope and saying what you thought it was. Now, of course, there is a range of monoclonal antibodies which will define whether the cells are of lymphoid or myeloid lineage and there are the cytogenetic changes, so we can say with confidence whether a leukaemia is lymphoblastic or myeloid. We are now able to comment more accurately on the occurrence of AML and ALL in children with DS and say that both types are increased but there are certain unique features.

Heinrich Hasle has recently published an excellent paper based on Danish data.\(^7\) This was a population-based study linking the population-based cytogenetic database with the children and adult cancer registries. It confirms an 18-fold overall increased risk of leukaemia in DS, no cases over the age of 29, and a very specific risk of myeloid leukaemia. Very interestingly there is a decreased risk of other cancers in all age
groups. Table 2 shows the overall incidence ratios and Table 3 shows the age-related incidence ratios for leukaemia. Looking at myeloid leukaemia there is an amazingly large standardized incidence ratio for children aged 0–4 (153). This is due to the dramatically increased risk of acute megakaryoblastic leukaemia – the same abnormalities as in the neonatal period, but occurring as a real leukaemia in the first few years of life.

**Management and outcome**

All children in the UK who get any type of cancer have their health records ‘flagged’ and the data are collected at the Childhood Cancer Research Group (a government sponsored group in Oxford run by Dr Gerald Draper). Therefore, there is vital information available on the survival of all children with every type of cancer in the UK and, because most children with cancer are treated at paediatric oncology centres, the United Kingdom Children’s Cancer Study Group can then link those records and see how many children are referred for treatment and how many of them are not.

In 1990, Dr Gill Levitt, working in our unit in collaboration with Charles Stiller, looked at children with DS and leukaemia between 1971 and 1986. We found that only 68% of those with DS and leukaemia (n = 98) were referred to a paediatric haematology oncology service, so that many were not being given specialist opinion and treatment at that time. We found that a lot of the children with lymphoblastic leukaemia were given suboptimal treatment and had a poor survival rate – much worse than those without DS. The survival for all children with acute myeloid leukaemia in the 1970s was about 15% and it was also poor for children with DS. So, up to about 20 years ago the children weren’t getting referred, they weren’t getting standard treatment and the results of treatment were very poor.

**Acute myeloid leukaemia**

*UK Children’s Cancer Study Group (UKCCSG) data*

Gill Levitt’s review of the 1971–86 data had shown that the results of treatment of AML were very poor for all children. One of the encouraging things that’s happened in the last 15 years is that for AML – the rare leukaemia in children, 60–70 new cases per annum – the survival has dramatically improved. It has improved from 10 or 15% to today where over half the children with AML can be cured largely by chemotherapy alone without bone marrow transplantation. When we looked at the patients at Great Ormond Street that we treated over quite a long period of time, the children with DS were doing better than those without DS. This is something that has
been experienced in a lot of units and study groups. At this stage we decided to look at how much children with DS nationally have benefited from these overall improvements in survival.

Janet Craze, therefore, reviewed the UKCCSG data for children for the years 1987–95. In this period there were 52 children with AML aged 12 months or more at diagnosis. Seven were not being treated; 13 were receiving individualized treatment and 32 were on standard protocols. Looking at all the children with myeloid leukaemia aged under 4 years (this gives a comparable group because myeloid leukaemia is rare in older children with DS), an overall relapse risk for the children without DS is 38% whereas the overall relapse risk for the children with DS is 12%. Their leukaemia is very sensitive to chemotherapy and very curable.

_The national childhood leukaemia trials – AML 10 and AML 12_

Our findings from the UKCCSG data made us concerned about the entry of children with DS into the national childhood leukaemia trials. There were two recent national trials for acute myeloid leukaemia (AML 10 and 12). These trials were examining the role of short-term (6 months) very intensive chemotherapy which, although it requires a lot of nursing and medical support in hospital, has proved to be very successful. Of the children in the trials, 4.7% had DS, compared with 9.8% in a recent US report, which suggest there is a reluctance to enter children with DS into these trials. If the children with DS and AML are compared to the others they tend to be younger – as expected with the dramatically increased risk in 0–4 year olds.

Myeloid leukaemia can be classified by looking at it under the microscope and using cytogenetics. It is classified by whether the leukaemia looks more like a monoblastic leukaemia or a megakaryoblastic leukaemia, or just ordinary myeloid cells, and given a number of 0–7 (a scale devised by a Franco-American-British group). In the trials it could be seen that children with DS didn’t tend to get the same morphological types of leukaemia as the other children and they tended to get megakaryoblastic leukaemia (M7).

Chromosome analysis in acute myeloid leukaemia is very important because certain cytogenetic abnormalities in the leukaemic cells predict for the children having a very good prognosis. Examples are translocation between chromosome 15 and 17 or 8 and 21. The children with DS and AML don’t have these translocations but despite this
they tend to do well.

Another feature of DS and AML is that it is quite an indolent disease. For example, one of our long-term survivors was born in Peru and his father, an engineer, took him to Miami before finding work in England, and we know that for about 6 months before he came to G.O.S. he’d had blasts in his blood. By the time he came to us he was getting anaemic and had bruising so it was clear that we had to intervene. He was treated and he did very well. With AML in DS you have plenty of time to think, to do your tests, and to discuss treatment but eventually in older children, (not of course the neonates), the disease will progress and without treatment the children will die.

If we look at the response to treatment (Table 4) in the AML 10 and 12 trials we find:

- Remission rate is not quite so good as for other children (83% vs 92%), but the difference is not statistically significant. The slight disadvantage is not because the leukaemia is resistant to treatment (5% vs 0%), but because of increased risk of induction death (17% vs 4%).
- Overall 5-year survival is the same as for other children (59% vs 60%).
- Relapse risk is significantly less than for other children (8% vs 39%).
- Risk of death in remission is significantly greater than for other children (21% vs 8%) because of increased vulnerability to infection during intensive chemotherapy.

The risk of increased deaths from infection during induction and remission mean that there has to be very good supportive care, very good nursing care and extreme vigilance because these children are vulnerable. They are vulnerable to death during their treatment – largely from infection – but if you can get them going and get them through that then they do well with a very good chance of cure and a very low risk of relapse.

In summary, management of TAM in the neonatal period is by observation only. In the older child with AML period progression is inevitable and, without treatment, death is inevitable, but the pace can be slow. Obviously we would suggest that you intervene once symptoms become apparent and once the children come to need blood products.

*Chemotherapy in AML*

The treatment results that have been discussed have been achieved by using very intensive cytotoxic chemotherapy. A very difficult question that has been debated
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Thursday 26 April 2001

worldwide, is whether such intensive chemotherapy is needed in DS and AML. I feel very dubious about this because I know that with previous non-intensive treatments these children didn’t do well. Dr Zipursky has treated some children with DS who have subsequently developed myeloid leukaemia with low dose cytarabine and has some long-term survivors. However, some of these patients have relapsed and it hasn’t been possible to rescue them (personal communication). We would probably need an international study to investigate whether low dose cytarabine is as effective as conventional treatment for children with DS and AML.

It is important to ask why these children respond so very well to treatment for myeloid leukaemia. Their blasts in culture are very sensitive to daunorubicin and cytarabine and children with DS and AML have more of the genes on chromosome 21 which modulate cytarabine metabolism. I can’t answer the question of whether there is a role for low-dose cytarabine therapy in children with DS and AML and I don’t think anybody else can honestly either.

So, in summary, children with DS get a unique form of myeloid leukaemia – megakaryoblastic leukaemia – which is very, very rare in other children. It is very sensitive to chemotherapy which is a very curative, but aggressive treatment. I should also mention that you don’t need a bone marrow transplant to cure these children – they do very well with chemotherapy.

Lymphoblastic leukaemia
As we’ve seen from the Danish and other data, ALL is increased in children with DS and we mentioned the poor treatment results from the 1970s and 1980s. Modern treatment for ALL comprises giving induction and intensification therapy to get the children into a stable remission and also giving treatment with lumbar punctures (previously with cranial irradiation) and intrathecal methotrexate to prevent leukaemic relapse in the spinal fluid. Then there is a long period (at least two years) of continuing therapy which is out-patient based where mercaptopurine and methotrexate are given by mouth. It is a long haul compared with the treatment for AML and during that long haul this period of continuing oral therapy is quite immunosuppressive. During this oral outpatient treatment which we call continuing or maintenance therapy patients may be at risk of ordinary childhood illnesses like chicken pox.

*The national childhood leukaemia trials – MRC UKALL X and UKALL XI*

Recently we looked at the entry of children with DS into the two recent national
Medical Research Council trials for acute lymphoblastic leukaemia, UKALL X 1985–1990 and UKALL XI 1990–1997, so there is about 15 years of data from modern treatment. There were 54 children (2%) with DS in the trials. More children were entered into the later trial than the previous trial – 1.9% as opposed to 0.9%. We feel there are still children who are not being treated on these trials, but the numbers entered have improved. If we look at the age distribution of leukaemia in the children with DS and compare them with the others we find that those with DS tend to be, as shown in the Denmark data, aged 2 to 9 years – they are not teenagers, adolescents or infants. If we look at the white cell count at presentation, which is often used as a prognostic predictor, there’s no difference between the two groups and there’s no difference in the low percentage of children who have blast cells in their spinal fluid. Lymphoblastic leukaemia is either a disease of early B cells (early BALL or common ALL) or early T cells (TALL). All these children with DS and leukaemia tended to get early B cell leukaemia or common lymphoblastic leukaemia – they didn’t get T cell leukaemia and that was supported in previous studies.

Cytogenetics is very important in predicting outcome in lymphoblastic leukaemia and one of the best predictors of outcome is high-hyperdiploid ALL. This is where the leukaemia has 50 or more chromosomes – this probably means that the cells are more able to take up methotrexate. The children with DS didn’t get high hyperdiploid ALL. There are some genetic changes like t(9;22) which is known as the Philadelphia chromosome, or t(4;11) which are associated with a poor prognosis – we think of bone marrow transplants in first remission for children with t(9;22). The children with DS didn’t get these adverse abnormalities either. The most common cytogenetic abnormality in lymphoblastic leukaemia is a translocation between chromosome 12 and chromosome 21 (the Tel/AML change). This can’t be picked up by routine cytogenetics – you have to use either molecular biology or FISH. The t(12;21) is common in children with ALL and you might think that that would be common in children with DS because of the involvement of chromosome 21. However, we only found it in one of the 15 patients with DS and ALL who were tested while it was detected in 127 of the 510 ALL patients without DS.

If we look at response to treatment in UKALL X and XI we find:

- For children with DS, the risk of deaths in the first remission fell from 21% to 8% from UKALL X to UKALL XI. For other children they fell from 4% to 2%. So the improvement over time is greater for those with DS.
- Overall 5-year survival for UKALL X and UKALL XI is good (73%) but significantly poorer than for other children (82%). UKALL XI figures are better
than UKALL X.

- Event-free survival in DS is 53% vs 63% in other children. This difference is not significant.
- Relapse rate by 5 years is 55% for DS and 34% for other children – again not significant.

We looked at treatment-related deaths during remission and found that they tended to be after long periods of neutropaenia when the children had been on long-term antibiotics. They tended to be fungal infections and looking at it critically, perhaps one should have introduced aggressive antifungal therapy with amphotericin earlier.

Although the relapse risk in most reports is similar, the overall survival for children with DS compared with other children was not quite as good as in some reports. We have learned that it is important both to deliver chemotherapy as intensively as possible but also to provide very good supportive care to reduce the risk of treatment-related deaths.

SUMMARY

In summary, infants with DS have macrocytosis and thrombocytosis, which appears to be something that doesn’t just happen in children with congenital heart disease. They have a varying degree of immunodeficiency and perhaps one of the manifestations of their immunological abnormalities is their predilection to develop leukaemia. Certainly another one is the problems they have with infections during treatment. They have an almost unique risk of transient neonatal abnormal myelopoiesis, and myeloblastic leukaemia and lymphoblastic leukaemia are more common. An increasing proportion, but still not all children with DS and leukaemia are now treated with standard protocols and it is encouraging that we can see improved survival and a decrease in treatment-related deaths. These children do have increased susceptibility to infections and need maximal supportive care, but I do feel that things are getting better.

We don’t know really why there is this increased risk of leukaemia in children with DS – perhaps if we better understood the nature of transient abnormal myelopoiesis and the spontaneous remission this would be clearer. We don’t understand the sensitivity to cytarabine and why there is a difference in the type of cytogenetic abnormalities in patients with acute leukaemia with and without DS. We don’t know what role chromosome 21 or genes on chromosome 21 have in leukaemogenesis but
we do know that many genes on chromosome 21 are involved in leukaemia. There’s the AML 1 gene which is involved in the t(12;21) – the commonest finding in ALL – and the t(8;21) in AML which is associated with a good prognosis. Then there are other genes involving tumour invasion and metastasis factor and in this region of chromosome 21 other genes. Somewhere in all this is the answer perhaps to why these children get leukaemia.
References

Question session

Cornelius Ani (Institute of Child Health) My question is regarding the use of methotrexate in the treatment of children with Down’s syndrome who have leukaemia. There is some evidence that when given standard doses of methotrexate that they suffer far more side effects.

Prof. Judith Chessells Yes, that’s true. It doesn’t mean you shouldn’t give them methotrexate of course, but interestingly enough in UKALL XI the children were randomised to methotrexate infusions at 6–8 g/m². We reviewed the records of all those children with Down’s syndrome who received high-dose methotrexate and there weren’t more complications – we thought there might be but there weren’t. It is true that sometimes they are more likely to get mouth ulcers and there are reports in the literature that they are more intolerant of methotrexate and that’s probably to do
with the genes on chromosome 21 involved in methotrexate metabolism. It doesn’t mean that you mustn’t give methotrexate – it means that you have to be cautious about it.

**Dr. Rosemary Guy (Derby)** I’m very interested in TAM which seems to have shown up in the last few years. You mentioned neonatal presentation – can it present at any other time?

**Prof. Judith Chessells** I know that some children with TAM have had persistent haematological abnormalities for a long time. I remember some years ago there was a famous child at the London Hospital who even after 8, 9, 10 months still had blasts in the blood – but eventually that child got better. There are one or two cases in the literature of TAM doing that, relapsing again – and then the child develops AML. I think what normally happens is that TAM is present in the neonatal period and it goes away at a variable rate. I guess that’s one of the reasons that I emphasise that there isn’t any rush to treat older children with apparent AML because, if it’s the tail end of TAM, it will get better and if it progresses then it’s obvious that you have to intervene. From the Danish and the MRC data we could see a cluster of patients in the neonatal or the first 1–2 months of life (a couple had been given AML treatment and, in retrospect, I don’t think that’s to be recommended) and then there’s another cluster which happens after about a year and that’s when it needs treatment.

**Dr Gupta (Hartlepool General)** My question is in context of TAM. Do you have any guidance regarding subsequent follow-up? Should it be fortnightly, monthly?

**Prof. Judith Chessells** I think that’s a very important question. What I have tended to do, but I’m only seeing the very complicated ones, is to suggest to the local paediatrician that they check the blood count about once a month for 2–3 months and then if it becomes apparent that everything’s fine just to do nothing. After all, continuing to do the blood count is not going to stop the children getting myeloid leukaemia later. I think it’s very hard on the parents and obviously one has to share this information with them. Now, with the increased literature, parents are very aware of this increased risk of leukaemia and the only truly useful thing that one can say is that it is very chemosensitive if it develops, and most children don’t develop it.
Table 1: Prospective study of blood counts in the first year of life in children with DS

- 25 infants during first year of life
- 64% were polycythemic for up to 2 months
- Haemoglobin pattern similar to other infants
- Age 9–12 months MCV and MCH elevated – normal erythropoetin levels
- No difference between babies with and without heart disease
- WBC and neutrophil counts in the low normal range
- Platelet counts raised from age 6 weeks to 12 months

Table 2: Overall cancer incidence ratios in children with DS

<table>
<thead>
<tr>
<th>Type</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer</td>
<td>60</td>
<td>50</td>
<td>1.2 (0.92 to 1.55)</td>
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<tr>
<td>Tumours</td>
<td>24</td>
<td>47.7</td>
<td>0.5 (0.32 to 0.75)</td>
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<tr>
<td>All leukaemia</td>
<td>36</td>
<td>2.04</td>
<td>17.6 (12.0 to 24.4)</td>
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<tr>
<td>ALL</td>
<td>20</td>
<td>.82</td>
<td>24.36 (14.0 to 37.0)</td>
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<tr>
<td>AML</td>
<td>12</td>
<td>.59</td>
<td>20.28 (10.0 to 35.0)</td>
</tr>
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SIR, standard incidence ratio; CI, confidence interval

Table 3: Age-related incidence ratios of leukaemia in DS

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<tr>
<th>Type</th>
<th>Age range</th>
<th>SIR (95% CI)</th>
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<tbody>
<tr>
<td>ALL</td>
<td>0–4</td>
<td>40.7 (22.7 to 67.0)</td>
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<td></td>
<td>5–29</td>
<td>12.4 (3.99 to 28.9)</td>
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<tr>
<td>AML</td>
<td>0–4</td>
<td>153.9 (73.7 to 283)</td>
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<tr>
<td></td>
<td>5–29</td>
<td>10.3 (1.16 to 37.2)</td>
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<tr>
<td>Total</td>
<td>All ages</td>
<td>17.6 (12.4 to 24.4)</td>
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SIR, standard incidence ratio; CI, confidence interval
Table 4: Outcome in children with DS and myeloid leukaemia in AML 10 and 12 trials

<table>
<thead>
<tr>
<th>Response to induction</th>
<th>DS (%)</th>
<th>Non-DS (%)</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Remission</td>
<td>83</td>
<td>92</td>
<td>p = 0.2</td>
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<tr>
<td>Resistant</td>
<td>0</td>
<td>5</td>
<td>p = 0.6</td>
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<tr>
<td>Induction death</td>
<td>17</td>
<td>4</td>
<td>p = 0.007</td>
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<table>
<thead>
<tr>
<th>Outcome at age 5 years</th>
<th>DS (%)</th>
<th>Non-DS (%)</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td>59</td>
<td>60</td>
<td>ns</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>59</td>
<td>51</td>
<td>ns</td>
</tr>
<tr>
<td>Relapse risk</td>
<td>8</td>
<td>39</td>
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</tr>
<tr>
<td>Death in remission</td>
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