Childhood acute lymphoblastic leukaemia

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INTRODUCTION

Cumbria has a significantly higher amount of childhood acute lymphoblastic leukaemia (ALL) cases diagnosed each year compared to the rest of the northwest of England. Inevitably, this has led to speculation that Sellafield, a nuclear reprocessing plant based in northwest Cumbria, has a part to play in the epidemiology. The aims are to explore the role of Sellafield in the ALL cluster and to design a leaflet for parents whose children have a suspected diagnosis of ALL at Furness General Hospital. Leukaemia accounts for one third of childhood cancers in the UK, with 79% of cases being ALL.[1,2] ALL in childhood is relatively uncommon with approximately 400 new cases being diagnosed in England each year, with the peak onset of 2-5 years of age.[1]

CHILDHOOD LEUKAUMIA: AN OVERVIEW

Childhood leukaemias are divided into lymphoblastic and myeloid, which are further divided into acute and chronic subtypes.[3] Lymphoblastic leukaemia is the malignancy of lymphoid cells and myeloid leukaemia is the malignancy of blast cells (monocytes and granulocytes).

The World Health Organisation (WHO) classification (as seen below) uses immunophenotyping to distinguish between sub-types.[4] This WHO classification is an improvement over the former FAB morphological classification. It has clinical and prognostic relevance.

World Health Organisation classification of ALL

- ALL / lymphoma (former FAB L1/L2)
  - Precursor B ALL / lymphoma cytogenic subtypes
    - t(12;12) (p12, q22) TEL/AML-1
    - t(1;19) (q23;p13) PBX/E2A
    - t(9;12) (q34;q11) ABL/BCR
    - T(V,11) (V;q23) V/MLL
  - Precursor T ALL/lymphoma
- Burkitt's leukaemia / lymphoma (former FAB L3)
- Biphenotypic acute leukaemia

PATHOBIOLOGY

ALL is a malignant disease caused by neoplastic proliferation of lymphoid progenitor cells with a B or T cell lineage.[3] Leukaemia is a monoclonal disease where a mutation in one stem cell leads to improper expression of oncogenes and/or a loss of function from tumour suppressor genes.[3]

There are alterations in the complex signalling networks which control cell death by apoptosis, cell proliferation and cell differentiation.[5,6] These changes are caused by modifications in the genetic material through chromosome translocations producing fusion genes, changes in the number of chromosomes (hypodiplodity and hyperdiplodity) and changes at a more subtle level from deletions of single nucleotide base.[6,7]

Each subtype of ALL is caused by a slightly different mechanism. The BCR-ABL type is caused by the translocations of the two genes BCR and ABL creating a fusion gene.[8] This new gene produces an active kinase enzyme that drives cell proliferation independently of other factors, including growth factor and mechanisms leading to apoptosis.[9] Normally the protein p53 induces apoptosis but the mutation leads to the cell being unresponsive to p53.[6]

The TEL-AML1 fusion gene is an example of a translocation producing a lack of cell differentiation. When the genes TEL and AML1 fuse abnormal proteins are produced, which inhibit cell differentiation by recruiting repressor molecules such as histone deacetylase enzymes.[6,10]

The biallelic deletion in the cyclin-dependent kinase inhibitor 2A gene increases cell proliferation.[11] This gene encodes for two tumour suppressors, which limit cell proliferation by inhibiting mitosis. If the tumour suppressor genes aren't present, mitosis is uncontrolled and the malignant cell continues to proliferate.[9]

PRESENTATION

The clinical symptoms and signs are a result of leukemic cells infiltrating bone marrow and the child's organs.

Bone marrow syndrome Anaemia	Weakness, lethargy, pallor, shortness of breath
Thrombocytopenia	Easy bruising, bleeding (eg nose and gums), petechiae, CNS bleeds causing spinal cord infarct or other CNS infarcts (rare)
Neutropenia	Febrile illness, often with prolonged or unusual course
Direct infiltration Hepatic/splenic	Hepatosplenomegaly may cause pain from capsule stretch
Medullary	Bone pain (may also have peri-osteal infiltration)
CNS	Headache, meningism, cranial nerve palsies, numbness of the chin
Testicular	Painless hard enlarged testis
Thymus	Superior vena cava syndrome with distended veins and facial/neck swelling, dyspnoea, cough (typical in T-ALL)
Other Leukostasis (WCC $>100 \times 10^9$ / litre) (very rare)	Poor perfusion of vital organs, pain from infarcts, priapism, visual disturbance

INVESTIGATIONS

Investigations confirm the diagnosis and search for any complications that may exist.[12] A full blood count should be done looking for signs of anemia and neutropenia. Then, a peripheral blood film should be performed which can be immunologically assessed via flow cytometry. Coagulation studies are needed to exclude disseminated intravascular coagulation. To rule out lysis syndrome, full serum biochemistry should be done, as well as liver function tests and a lactate dehydrogenase test. Uric acid levels maybe raised due to rapid cell turnover. A chest X-ray can be done to rule out mediastinal involvement, pneumonia and lytic bone lesions.

A bone marrow aspirate should be performed and sent off to clarify which type of ALL the patient has and tested using:[13]

- morphology
- immunophenotyping – to clarify the phenotype
- cytogenetic and molecular cytogenetic analysis – including standard G-analysis and FISH (fluorescence *in situ* hybridisation) tests to confirm the genotype

TREATMENT

As well as pre-treatment assessment, during and after therapy monitoring is needed to detect any complications. Treatment tends to last for 2-3 years, approximately two thirds of cases can be treated successfully within the first 12 months, but prolonged treatment is associated with a better prognosis and smaller chance of relapse.[3] Before starting treatment patients are risk assessed to estimate their chance of relapse, influencing the treatment the child receives. High-risk patients are given more intense treatments, to reduce risk of relapse. It's important to establish risk because intense therapy leads to higher risks of treatment-related complications. Risk is based on age, leukocyte count and ALL subtype.[9]

The phases of treatment are:

- intensive remission-induction
- consolidation
- re-induction/delayed intensification
- maintenance chemotherapy

The remission-induction phase aims to eradicate 99% of the leukemic cell burden to help restore haemopoiesis to its normal function and performance states. The delayed intensification targets drug resistant leukemic cells to prevent relapse. Consolidation is a maintenance therapy to make sure haemopoiesis stays at normal function and to irradiate further cancerous cells to prevent remission.

Multiple drug use is used to avoid treatment resistance. Most therapies use a variety of three drugs, whereas higher-risk cases use a combination of four drugs. Higher-risk cases may be treated with an allogenic haemopoitic stem cell transplant.[9]

PROGNOSIS

Out of all childhood cancers leukaemia accounts for 30% of deaths, but has a cure rate of 75%.[6] The three factors affecting the prognosis are the leukocyte count, the child's age and the subtype of ALL.[9] Higher leukcoycte counts increase the risk of earlier complications such as a CNS haemorrhage.

Studies have shown that there's an age-related affect. Children ages 1-9 have an 88% chance of a five-year event-free survival, children between 10-15 have a 73% chance, but babies less than 12 months only have a 44% chance.[9]

A study at St Jude Children's Research hospitals showed patients with hyperdiploidy (>50 chromosomes),TEL-AML1 fusion and t(1;19)/E2A-PBX1 fusion had a more favourable outcome compared to children with the t(9;22)/BCR-ABL fusion or the t(4;11)/MLL-AF4 fusion type.[9]

SURVEY OF EPIDEMIOLOGICAL DATA

Results for the number of cases of ALL in England, the North West Strategic Health Authority (SHA) and the Cumbria Primary Care Trust (PCT) were gained from the National Cancer Information Services (NCIS). Information was used from 2005-2009 to get some of the most recent data. The North West SHA figures were divided by 24 (the number of PCT's in the North West SHA) to give an average. A similar calculation was made for working out the average number of cases in the ten SHAs in England.

PubMed was accessed to find articles for the literature review. The articles had to meet the following criteria:

- include Sellafield
- be a UK-based study
- the article had to focus on a single study. Literature reviews and meta-analyses were excluded
- focused on nuclear installations and geographical location not the effects that radiation may have on a child or the population, eg population mixing or effects of radiation on conception
- investigates a childhood group anywhere from 0-15 years old

The table below shows the search phrases used.

Search phrase	Total results found	Relevant results	Number of new results
("Leukemia [MESH] AND "radiation" [MESH] AND "Nuclear Power Plant" [MESH]) AND "Sellafield"	0	0	0
("Leukemia [MESH] AND "radiation" [MESH]) AND "Sellafield" AND "childhood"	6	2	2
"Sellafield" AND "childhood" AND "leukaemia"	39	3	1
"Sellafield" AND "childhood" AND "leukaemia" AND "Nuclear" AND "Radiation"	29	3	1
"Nuclear" AND "radiation" AND "leukaemia" and Sellafield"	50	4	0
"Nuclear" AND "radiation" AND "Leukaemia" AND "England"	88	4	1
"Nuclear" AND "installations" AND "Leukaemia" AND "England"	15	5	1
Total			**6**

From the six relevant results, two articles didn't meet the inclusion criteria.[14,15] Each study will be critically analysed to conclude if results were reliable.

RESULTS

Below is a table showing the number of cases of ALL in children 0-14 years old from the years 2005-2009 in the North West SHA and in the Cumbria PCT. An average was taken to compare Cumbria's rates to the rest of the North West.

Year	Number of new ALL cases in North West SHA	Average number of ALL cases in North West PCTs	Number of new ALL cases in Cumbria PCT
2005	60	2.5	5
2006	59	2.5	1
2007	39	1.6	3
2008	45	1.9	6
2009	65	2.7	7
Total	268	11.2	22
Cancer Incidence :ICD10:C91-95 Leukaemia. Source NCIS			

Here is a table comparing the average number of cases diagnosed in SHAs in England compared with the North West SHA.

Year	Number of new ALL cases in England	Average number of cases in England per SHA	Number of new ALL cases in North West SHA
2005	400	40	60
2006	412	41.2	59
2007	374	37.4	39
2008	383	38.3	45
2009	420	42	65
Total	1,989	198.9	268
Cancer Incidence :ICD10:C91-95 Leukaemia. Source NCIS			

DISCUSSION

The North West SHA on average has a higher number of cases of ALL each year compared with the rest of the SHAs in England. Apart from 2006, Cumbria has a higher number of cases diagnosed each year compared with the average of the North West's PCTs. One possible explanation could be the influence of Sellafield nuclear reprocessing site.

The 1984 Black Report suggested that Sellafield was responsible for the leukaemia cluster.[16] To investigate this further a literature review has been carried out. Four journal articles were found that investigated the association between Sellafield and childhood leukaemia.

Goldsmith[17]

This was a case-control study to investigate the association between nuclear installations and childhood cancers in 0-9 year olds. It took place between 1971 and 1980, and used incidence and mortality rates as the main outcome measure. Standard mortality ratios (SMRs) and standard incidence ratios (SIRs) were used and contrasted against an estimated SMR/SIR. The study looked at 21 nuclear installations and compared SMRs and SIRs in the surrounding communities. Data were collected from cancer registries and group local authority areas. Overall, the results showed no association between nuclear installations and childhood cancers. However, there was a significant increase according to 'pc criteria' (a specific binomial coefficient) of leukaemia in Sellafield, showing a weak link between the two. Goldsmith acknowledges that there is an increased number of cases and admits that he doesn't know whether it is because of a causal relationship.

Strong points of this study were that SMRs and SIRs were calculated taking into account population differences in each community, and each studied community was paired with a control community which was matched in location, population size and urban/rural characteristics to avoid confounding. Weak points were only investigating incidence and mortality rates in 0-9 year olds because childhood cancer is classed from 0-14 and the study only looked at the largest-populated community near the installations. This could be improved by comparing incidence and mortality in different geographical areas marked by particular boundaries, eg 5km, 10km and 25km away. Other tests, such as P-values and confidence intervals, could have been used as a test of statistical significance.

Draper *et al*[18]

This study investigated cancer in Cumbria in relation to Sellafield from 1963-1990. Ages 0-75 were included, with the main emphasis on 0-24 year olds. Data were used from population-based registries and using specific surveys. The expected rates of ALL were calculated using the national figures and compared with the observed figures. Like the previous study, SIRs were calculated. Incidences were compared in three groups: Seascale, the districted closest to Sellafield; Allerdale and Copeland, the two districts nearest Seascale; and the rest of Cumbria. The results showed that in the 0-14 age group the incidence was higher in Seascale compared to the rest of the districts, supporting the hypothesis that proximity to Sellafield affects ALL rates. To further support this, further P-values were very low, implying the results were statistically significant.

Advantages of this study were that it compared incidences all over Cumbria to measure a dose-related response and used SMRs and SIRs to make a comparison. P-values were calculated to show the probability that the results were down to chance. The study was carried out over 27 years, allowing more data to be collected because ALL is fairly uncommon, making this study more reliable. Weaker elements were not having a control group and, therefore, making the study liable to confounding factors.

Bithell *et al*[19]

This had focused on the proximity of residence to nuclear installations and the incidence of leukaemia. Twenty-three nuclear installations were investigated against six control sites from 1966-1987. Expected numbers were calculated and compared with the observed numbers to form a ratio. Incidence was measured in electoral wards within 25km of the installation. Incidences of children 15 and below with a registered diagnosis of leukaemia were studied. Overall, no relation was found; the only significant result was Sellafield, with an observed-to-expected ratio of 1.30 with a P-value of 0.0002. This only showed a very weak relationship and the authors concluded that it didn't show a casual association of geographical location and the installation. They suspect that this increased incidence was caused by something else, ie

paternal radiation during conception rather than direct radiation to the child. This was a hypothesis explored by a 1993 study.[20]

Strong areas of this study were the uses of statistical tests. Bithell realised that malignancy in children is rare and that numbers are generally small, so he explored many hypothesis tests and researched the most powerful test to use for this situation. He used a linear risk score test, which is a form of ranking that can detect spatial correlations. They also had an outcome measure of 5% excess as a baseline increase to show if any increases of incidence were statistically significant, which other studies haven't done. Weak points are the use of only six control sites; it didn't say whether they were matched or not. To test the geographical association, the 25km area surrounding Sellafield could have been divided into smaller zones.

Cartwright[21]

This study's objective was to formally investigate the onset of the Seascale cluster of childhood cancer. Findings were based on mortality rates from 1906-1970, investigating the effects before and after Sellafield was built. Data were collected from the Whitehaven registration district and compared with Seascale, Gosforth and the rest of Whitehaven. The study looked at ages 0-84, with a separate group for ages 0-14. The study showed there was an increase in mortality from 1956-1965 (three deaths in the Seascale district), but showed no excess in 1967-1970 or before Sellafield was built. The rest of Whitehaven didn't show any statistically significant increase in figures either. The study concluded that there was no temporal relationship between leukaemia and Sellafield. There were only three deaths due to leukaemia after the plant was built in the nearest community to Sellafield. This could have been for a number of reasons including a change to the population structure brought by workers moving to the area or it could be coincidence. Either way the numbers are too small to show an association.

Comparisons made before and after Sellafield was built are commendable because they rule out other possible causes of leukaemia and show us if leukaemia was already prevalent before Sellafield's arrival. Other strong points were its use of confidence intervals as a test of statistical significance. Weak points were having no control group and using comparison communities with incredibly small populations, like Gosforth. Mortality data was used which could be considered as an unreliable outcome measure because in the 1960s treatment of leukaemia improved dramatically leading to less deaths. This wouldn't give a true representation of leukaemia rates. Incidence would have been a more accurate measure.

CONCLUSION

Three studies showed that there is an association between leukaemia and Sellafield; however, Bithell's association is so weak that that result has been rejected.[17,18,19]

Overall, the literature shows a weak association which doesn't prove a causal affect. The studies investigated all had flaws in their study design; however, no study was so unreliable that its findings were rejected. The results support there being a cluster in Cumbria, as pointed out by other researchers, but this cluster could be there for reasons other than Sellafield.

The three studies that looked at nuclear installations throughout the UK generally didn't show an association between nuclear installations and leukaemia, with Sellafield being the exception to the rule.[17,18,19] Other possible causes of higher rates of leukaemia could be from population mixing, parental exposure to radiation, social class structure or infection.[20, 22-25] The cluster may not result from direct radiation to the child and could be caused by parental exposure to the radiation during conception.[22]

Only four studies were found that met the criteria, showing that this area hasn't been researched enough. The association has been explored from 1906-1990, which suggests more recent research needs to be carried out using incidence rates. Now that the investigation and management of childhood leukaemia has been more established, it's the ideal time to research the association. A case-control study should be performed with matching for age, gender and social structure. The area around Sellafield can be divided into concentric ringed zones – 0-5km, 5-10km, 10-20km, with the main aim of investigating ALL in relation to the proximity of Sellafield. Studies performed in other parts of Europe have used methods similar to this.[26-28] Incidence can be measured over these four zones where SIRs are calculated to allow comparison. This would be a strong study design to compare the association between childhood leukaemia and the proximity to Sellafield. ALL subtypes could be confirmed in each case to see if Sellafield gives risk to a particular type.

Compared to the other SHAs in England, the North West SHA on average has a higher number of ALL cases diagnosed each year. This too could be investigated because it raises the question 'Is Cumbria's higher incidence due to Sellafield or is it a result of a bigger issue affecting the whole of the North West?' These results were found on taking averages and, therefore, aren't very reliable, but a future recommendation is to explore this pattern more and investigate possible causations.

It has been concluded that there is a cluster of ALL in Cumbria; however, there is very little evidence to support Sellafield as a direct cause. The association is too weak to justify any actions to move people away from nuclear reprocessing sites. However, in future studies if the relationship is stronger than originally thought, future nuclear reprocessing sites should be built a specific distance away from populations/settlements for the safety of the people living there.

LEAFLET

In 2009, four children were admitted to Furness General Hospital in South Cumbria with ALL, who were then referred to Manchester children's hospital. Manchester has a tertiary centre with all the resources needed to investigate and treat ALL effectively. For parents this is understandably a stressful time where they are bombarded with new information about ALL and their child. A leaflet explaining the situation and what the parents can expect in the near future could prove useful. A leaflet has been developed to try and help parents at this difficult time which they can read at a moment which suits them. See figure 1 for a copy of the leaflet.

Acute Lymphoblastic Leukemia

WHAT IS LEUKAEMIA?

Leukaemia is cancer of the blood. Acute lymphoblastic leukaemia (ALL) affects the T and B white blood cells. These cells make up your immune system and help fight infection. In ALL the T and B cells multiply at faster rates and don't mature properly making the immune system less effective. The cells build up in the bone marrow and other organs and can affect how they work. This can lead to anaemia causing tiredness and breathlessness, blood clotting problems and serious infection.

ALL can happen at any age, but peak onset is at 2-5 years old.

HOW OFTEN DOES IT OCCUR?

- Acute Lymphoblastic Leukaemia accounts for one third of childhood cancers.
- It is relatively uncommon with about 400 new cases being diagnosed each year.
- Approximately 2 cases are diagnosed at Furness General Hospital each year.

WHAT HAPPENS NEXT?

After the diagnosis has been confirmed with blood tests and scans your child will go to a tertiary healthcare centre. This is a specialised unit it which has the expertise and resources to give your child the best possible care and treatment.

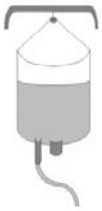
In this area most children go to The Royal Manchester Children's Hospital.

TREATMENT

Treatment regimes vary and depend on the type of leukaemia the child has. The aim is to kill all of the abnormal cells so the bone marrow can start working properly again and so it starts producing normal cells. Leukaemia normally is treated with chemotherapy and sometimes this is combined with radiotherapy.

Chemotherapy is where anti-cancer drugs are used to kill cancer cells and stop them dividing rapidly. Radiotherapy is were ionizing radiation is used to kill or control cancer cells. .

Treatment lengths can vary but it tends to last 2-3 years long. This is to make sure all the cancer cells are killed and to prevent the risk of it coming back.

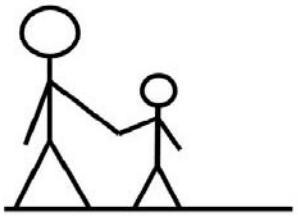


AFTER TREATMENT

Recent data has shown that the cure rate for leukaemia is 80% however 1 in 4 children's leukaemia come back. If this is the case they have more treatment similar to what they had the first time around.

Approximately 70% of children have a five year event free survival. But most children go on to live a normal life after there leukaemia has been treated.

After treatment your child will still need to see doctors as a follow up and to check how things are going.



FURTHER HELP AND INFORMATION

Macmillan Cancer Support
A supportive group that helps anyone affected by cancer.
Web: www.macmillan.org.uk
Tel: 0808 800 1234

Leukaemia and Lymphoma Research
www.leukaemialymphomaresearch.org.uk/
They provide information on Leukemia and the latest research.

Leukaemia Care
Tel: 08088 010 444
Web: www.leukaemiacare.org.uk
Provides 24 hour care and support as well as a good source of information for Leukaemia

Cancer Help UK
Web: http://cancerhelp.cancerresearchuk.org/
Gives facts about cancer including causes, incidence and treatment choices

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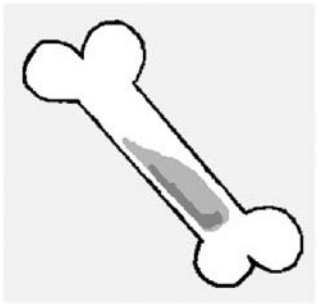
2012

A QUICK GUIDE

Acute Lymphoblastic Leukemia



A Guide for Parents

Figure 1 – Leaflet for parents

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