Introduction

Acute lymphoblastic leukemia (ALL) is a type of cancer that affects white blood cells. These cancerous lymphocytes inhibit normal bone marrow function, leading to anaemia and infection. 0.1% of ALL patients harbour a MYC rearrangement with B-cell precursor ALL (BCP-ALL)\(^7\).

Treatment of ALL considers a range of prognostic factors such as white cell count (WCC), age, immunophenotype and cytogenetics, which stratify patients into low, medium or high risk groups (Figure 1).\(^1\) Mature B-ALL treatment involves a short and intensive regimen of chemotherapy (with high-dose methotrexate, cytarabine and cyclophosphamide).\(^7\) BCP-ALL treatment includes induction and maintenance therapy given over 3 years for boys and 2 years for girls.

MYC is an oncogene that is overexpressed in Burkitt’s lymphoma (BL), where it has been shown to be essential for BL cell survival and proliferation.\(^1\) The aberrant expression of MYC arises from a translocation between chromosome 8 and the immunoglobulin heavy (Igh) or light chains (Igl or Igk) respectively; t(8;14), t(2;8) and t(8;22).

As evidenced in Figure 1, the characterisation of genetic rearrangements in ALL has prognostic value. The aim of this study was to characterise BCP-ALL patients with suggested involvement of MYC. MYC involvement was to be confirmed, additional clinical data gathered and a literature review to be completed in order to future decisions on the optimum clinical approach for patient treatment.

Methods

Forty seven patients were identified from a patient database that has a cytogenetically visible abnormality in the region in which MYC resides on chromosome 8 (8q24).

Fluorescence in situ hybridization (FISH) was performed on patients with fixed cells to verify the presence of the MYC translocation.

FISH uses oligonucleotides with fluorophores attached or “fluorescent probes” to bind to specific gene sequences on the chromosome. With the MYC breakapart probe (CytoCell), a red and green probe is designed to bind to opposite ends of the MYC gene as seen in Figure 2. A summary of the FISH process is shown in Figure 3.

Results

- Sixteen patients were identified to have MYC rearrangement as seen in Table 1. A further 8 patients were deemed positive due to t(8;14) and t(8;22) being observed in their karyotype. Sixteen were paediatric patients (range 0-17 years old) and 8 adult patients (range 28-64 years old) altogether. The most prevalent translocation observed was the t(8;22), an IgL-MYC translocation, seen in eleven patients.
- Of the twelve paediatric patients confirmed by FISH (Table 1), eight had survival data available. 6 patients were still alive 3 years post diagnosis. Insufficient data was available from adult patients to draw any conclusions. 1 patient died from primary organ failure and another never achieved complete remission (CR) upon treatment.
- Of the sixteen patients, an average of 57% of cells exhibited a breakapart signal pattern as seen in Table 1.
- No significant difference was seen between the MYC-positive and MYC-negative patients in terms of immunophenotype (Table 2) or length of time from diagnosis to death.

Discussion

- This is the largest study to investigate MYC rearrangements in BCP-ALL to date.
- Twenty four patients were confirmed to be MYC positive by FISH. The most common translocation was t(8;22) whereas a previous study\(^6\) found the t(8;14) translocation to be most prevalent.
- Outcome data show a trend towards a favourable outcome in the MYC positive patients reported here, however this warrants further investigation in a larger cohort in order to understand the impact the MYC rearrangement has on the prognosis.
- Other confounding factors may contribute to the outcome of these patients including other cytogenetic abnormalities, age, WCC, response to treatment, presence of minimal residual disease and additional gene deletions.\(^6\)
- Immunophenotype data collected on this cohort shows that all patients have positive staining for B-cell markers. Interestingly, both positive and negative patients also show positive staining for T-cell and myeloid markers.
- In a previous study of 5 paediatric patients, upon discovery of a MYC rearrangement, these patients were switched to a mature B-ALL treatment protocol. All patients achieved complete remission. The patient cohort we studied received BCP-ALL treatment with no protocol switch, but also showed a trend towards a favourable outcome.
- Further studies will be conducted on an expanded patient cohort to include confirmation of BCL2 (green in Table 1 and BCL6 involvement, alongside single nucleotide polymorphism arrays to investigate copy number alterations present in the genomes of these patients. The intention is to expand our knowledge on this rare subgroup of BCP-ALL patients.

References and Acknowledgements


