Volume 9, Issue 10, October – 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT1931

The Role of Immunotherapy in ALL and its Impact on Healthcare

Mahin Amir
Imperial College London

Abstract:-

- ***Background***

ALL is a rare but aggressive malignant cancer caused by uncontrolled proliferation of lymphoblasts which disrupt normal organ function.

- ***Review of Interventions***

In this article we will discuss how genomic medicine allows better risk stratification and early identification of certain genetic alterations. Different immunotherapies will be reviewed, their mechanism of action and novel upcoming therapies.

- ***Assessment of Impact***

The addition of immunotherapy has improved clinical outcomes for patients, increasing overall survival and having a lower AE profile.

- ***Conclusion***

Immunotherapy offers a more targeted approach in ALL management, despite high initial costs, it can prove to be cost-effective and inevitably reduce burden on a health system.

Keywords:- *Immunotherapy, Chemotherapy, Monoclonal Antibodies, Leukemia, Healthcare.*

I. INTRODUCTION

Acute Lymphoblastic Leukaemia (ALL) is a malignant blood cancer where the lymphoid progenitor cells in the bone marrow undergo uncontrolled proliferation to become 'leukaemic lymphoblasts'. These lymphoblasts go onto infiltrate multiple organs resulting in disruption of normal body function. Although we understand lymphoid progenitor cells undergo genetic alteration which causes ALL, we still do not know what causes these mutations. There are 2 major subtypes of ALL – precursor B-cell (being the most common) or T-Cell. The T-Cell is the more aggressive one of the two having a higher prevalence in adults than children. Although rare, The American Cancer Society estimates 6540 new cases of ALL (3660 in males, 2880 in females) in the US in 2023 with the highest risk population being under 5 years of age [1].

The treatment of ALL is urgent and the primary goals of management are induction, consolidation, maintenance, and CNS prophylaxis. The purpose of induction therapy is complete remission, to destroy leukaemic cells, reduce or eliminate clinical symptoms and for blood cell values to normalise. This is typically achieved by using a combination of chemotherapy drugs (vincristine, dexamethasone, anthracycline) and require hospitalisation. Consolidation therapy is the continuation of these drugs which can last for several months to ensure ongoing remission and finally the purpose of maintenance therapy is to prevent the ALL from returning. ALL can frequently recur in the cerebrospinal fluid (CSF) and to prevent this relapse they require intrathecal chemotherapy. Stem cell transplantation is a treatment viable for patients with abnormal cytogenetics, chromosomal abnormalities (translocation of chromosome 4 & 11) or other high-risk features of ALL. However, these are associated with significant adverse events such as Graft vs Host Disease [2].

Genomic medicine has impacted the way ALL is treated. Using techniques such as flow cytometry to detect Minimal Residual Disease (MRD) and quantitative PCR of Leukaemia specific genes (BCR-ABL1) has allowed early identification of the subtypes of Leukaemia which are likely to be more aggressive and resistant to chemotherapy, as well as improve the way we risk stratify these patients. Therapies have emerged which have specific molecular targets. Some of these include targeting JAK2, EPOR and TYK2. These therapies have advanced the management of ALL [3].

In this traditional review of literature, we will discuss some of the immunotherapies used in managing ALL and critically evaluate the existing evidence-based literature involving these therapies, comparing their strengths and limitations to chemotherapy as well as discuss the impact it has had on a national health service. We will also discuss some upcoming novel therapies and how these can potentially add to the remarkable success which has been achieved in managing ALL.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT1931

II. BACKGROUND

The use of immunotherapy first emerged into the field of oncology back in 1986 with the approval of IFN-a2 by the FDA [4]. Since then, the use of many monoclonal antibodies (MABs) has been approved and they have been the mainstay of current cancer treatment. This has further developed into 'targeted immunotherapy' to give an even more individualised approach to managing cancer based on their genetic material.

Antibodies are proteins which are made by the body in response to fighting foreign substances. They attach to another protein called an antigen, and once attached can signal the body to engulf or destroy the foreign substance. MABs are man-made proteins that can be designed to target specific antigens such as those found in cancer cells and thus aid in fighting the cancer. There are two ways in which MABs can support the immune system. One is a more generic approach acting like immunotherapy which helps the body in identifying and killing cancer cells more effectively. Another method is often referred to as 'targeted therapy'. This is when MABs are designed to attach to a cell-specific antigen of a particular cancer allowing the body to have a more focussed approach. The proteins for these MABs can be derived from humans, animals, or both. They can be conjugated (covalently linked to a cytotoxic drug) or unconjugated.

III. INTERVENTIONS:

Rituximab is a chimeric MAB which specifically targets the surface antigen CD20 which is found in 30% – 50% of precursor B-Cell Lymphoblasts [5].

Studies published from 2012 – 2016 have reported the addition of Rituximab to the chemotherapy regimen for patients with B-lineage ALL have improved the outcome for CD20+ Ph-negative ALL [6][7]. However, not every patient will be entitled to the addition of Rituximab. Since it specifically targets the surface antigen CD20, most protocols restrict the use of Rituximab only for those who have an expression of CD20>20%. Thomas et al evaluated the addition of Rituximab has improved outcomes for patients with Burkitt ALL [8]. Another study has shown the same for pre-B ALL [9]. These studies were not RCTs, and the population sizes were relatively small. However, similar conclusions were drawn, the addition of Rituximab to chemotherapy regime improves clinical outcomes.

Although Rituximab has revolutionised the management of CD20+ malignancies, it does also cause side effects. These include infusion related reactions, Tumour Lysis Syndrome, Infections, Neutropenia, Progressive Multifocal Leukoencephalopathy, Hypogammaglobulinemia as well as some cardiac events such as Myocardial Infarction and Arrhythmias [10][11][12].

Philadelphia +ve (Ph+) ALL is a subset of ALL which is caused by a reciprocal translocation between the ABL1 gene on chromosome 9 and the BCR gene on chromosome 22 – denoted as t(9:22) (q34:q11) in cytogenetic studies. This new fused gene is oncogenic and codes for BCR-ABL1 Tyrosine Kinase. The BCR-ABL1 causes leukaemia by activating a cascade of signalling pathways which trigger certain transcription factors (STAT, RAS, PI3K, FAK) leading to increased cell proliferation and disruption of normal cell differentiation. Tyrosine Kinase Inhibitors (TKI) are a cornerstone in the management of Ph+ ALL as they inhibit the BCR-ABL1 Tyrosine Kinase. Imatinib was amongst the first TKI to be used in Ph+ALL leading to complete remission rates exceeding 90% [13]. A major drawback with TKIs has been patients developing resistance to it due to mutations in the BCR-ABL1 gene and hence limiting the efficacy over time. Since Imatinib, other TKIs have emerged, these include but not limited to Nilotinib, Dasatinib and Bosutinib. Asciminib is one of the latest TKIs currently under investigation for its use in Ph+ALL with a phase I trial underway to test its safety (NCT03595917).

Bi-specific T-Cell engager (BiTE) antibodies are those that can bind to antigens on tumour cells and simultaneously to CD3 on T-Cells. This results in T-Cell activation and then tumour lysis. Blinatumomab is a MAB with these bi-specific properties and has been a hallmark in ALL management as it spares healthy cells and targets cancer cells more specifically [14]. A pivotal trial that explored the clinical efficacy of Blinatumomab was the TOWER trial – a phase III trial involving adults with Ph-ve relapsed or refractory B-cell precursor ALL which illustrated Blinatumomab extended overall survival by 3.7 months [15]. In the same trial it was evaluated that adverse events grade 3 or above were lower in the Blinatumomab group in comparison to chemotherapy (87% vs 92%) [16]. If further research and trials can explore how to mitigate the side effect profile of Blinatumomab then this can remarkably improve patient care and reduce burden on the healthcare system.

Programmed Cell Death Protein-1 (PD-1) is a protein which is a cell surface receptor on T and B-Cells. It functions in the immune system by acting as an inhibitor in the adaptive and innate immune response [17]. This can be beneficial as well as harmful. The benefit of PD-1 is that it can aid in immune tolerance by down-regulating some immune responses. Conversely, it can interfere with the protective immune response against cancers by causing further dilation of malignant cells in the body [18]. Inhibition of the PD-1 receptor has been proven to be effective in anti-tumour immunity.

Zeluvalimab (AMG404) is a novel therapeutic MAB which specifically targets PD-1. It is currently under investigation for its use in managing ALL. AMG404 which belongs to class of BiTE can help the immune system to target cancer cells specifically. It is structured to engage the T-Cells and take them to the site of the cancer, enhancing the efficacy of the immune response. CD3 is expressed on T-Cells and CD19 is expressed on Leukaemia B-Cells. The dual binding property of AMG404 creates this immunological passage between the body's own immune cells and cancer cells which leads to the activation and subsequent destruction of the malignant B-cells. By using

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT1931

the body's own immune system, AMG404 offers a more targeted approach in treating ALL. There is currently a phase I trial which is evaluating the safety and efficacy of this novel therapy [19]. Like with other immunotherapeutic agents, the use of AMG404 comes with side effects. These mainly include Cytokine Release Syndrome (CRS) and Neurotoxicity. How to mitigate these side effects as well as manage them are currently ongoing areas of research. Although, AMG404 offers a promising approach to managing Leukaemia and potentially an integral part of the treatment landscape, it is important to acknowledge the limitations of the data available. Further research and clinical trials are imperative to better understand the full potential as well as the limitations.

Chimeric Antigen Receptor T-Cells (CAR-T) is a therapy in which the patient's own T-Cells or Natural Killer cells are genetically altered to express a chimeric receptor which recognises specific antigens expressed by tumour cells. There have been 4 generations of CAR-T produced up till now, each with a more defined domain and increased efficacy than the previous. Clinical trials have been conducted to evaluate the use of CAR-T cells in the treatment of haematological malignancies including ALL. These trials have concluded that CAR-T showed remarkable results in children with recurrent or resistant disease. Although, the study size was small (30) they have formed these results as the basis for further research [20][21]. As with other immunotherapies, CAR-T carries a significant risk of CRS. These risks need further evaluation and research.

IV. IMPACTS ON HEALTHCARE:

We have discussed in the article the implications of immunotherapy for patients, but how does it impact a national health service?

We will use the National Health Service (NHS) as the healthcare system for reference to discuss the impacts of immunotherapy.

A metanalysis of 7 RCTs by George et al reported the Relative Risk (RR) of toxic adverse events in MABs was much lower than chemotherapy. Additionally, the percentage of treatment discontinuation was higher in chemotherapy than immunotherapy (11.1% vs 4.5%) [22]. It can be argued that patients who discontinue treatment early are likely to re-present to hospital in a poorer clinical state which would require additional use of resources – increasing the burden onto a very strained public health system. Further, with chemotherapy having a higher Adverse Events (AE) profile this could illustrate the need for longer hospitalisation and interventions which would again add to the costs on the NHS.

On the contrary, studies have also identified that managing the AE for chemotherapy is more familiar and habitual to clinicians than managing the AE for immunotherapy. A need for education on early recognition/management and MDT approach on managing the AE for immunotherapy was also highlighted in the study [22]. If achieved, in the long run this could help ease the load on the NHS.

Magee et al published a meta-analysis in 2020 which compared the AE of chemotherapy vs immunotherapy across 22 trials involving 12,727 patients in which they compared patients developing an AE ≥ grade 3 in severity. They found that in the chemotherapy group AE were reported more by 24.59% than the immunotherapy group. Fatigue, diarrhoea, and AKI were more prevalent in the chemotherapy group, but colitis, pneumonitis and hypothyroidism were more common in the immunotherapy group [23]. This highlights the need for further research which compares hospital admission stay/re-admission of those with chemotherapy-induced AE and those with Immunotherapy-induced so that an estimate usage of resources can be produced.

The cost of immunotherapy is high. In 2018 NICE reported that the average cost of treatment with Pembrolizumab was £84,002 [24]. Zhang et al conducted a systematic review of 24 studies in 2022 in which they found Pembrolizumab was cost-effective in the US but not in the UK [25]. Perhaps this disparity across regions exists due to different protocols and methodologies of research. From this we can also infer that despite high initial costs of immunotherapy, in the long term it is plausible to assume that it can be more cost-effective than chemotherapy as proven in the US.

Despite the advancements of immunotherapy, there are disparities that exist in treatment delivery due to socioeconomic factors. Studies have been published that report mortality due to cancer is greater in the most deprived areas. In 2018, Scotland reported that the mortality due to cancer (all types) was 32% higher in the most deprived areas than the least deprived [26]. We were unable to find any studies that could compare the socioeconomic disparities in the UK for ALL. Bhayat et al evaluated a cohort study for AML patients from the year 1998 – 2007 involving 23,910 patients in which they established patients were 40% less likely to receive Bone Marrow Transplantation in comparison to the most advanced group (Odds Ratio 0.60, 95% confidence interval 0.49, 0.73) if they were amongst the deprived socioeconomic quintile [27]. This highlights the need for further studies to help identify the reasons behind these inequalities to ensure equal access across the UK to a public health system.

V. CONCLUSION

Genomic medicine has had a global impact in the way management of ALL is now approached. Early identification of certain genetic alterations and the use of MRD has altered the classification and risk stratification of ALL. Using these techniques has allowed clinicians to formulate more effective management plans that confer an individualised approach. Immunotherapy has been one of the major breakthroughs and its use has shown superior clinical outcomes for patients. Upcoming novel therapies suggest a

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT1931

promising future for patients with ALL. Studies evaluated in this article also highlight the limitations of immunotherapy and which aspects require further research.

The impacts of immunotherapy on a national health service have been explored and why investing further time and resources into this research can potentially prove to be beneficial for the patients as well as the NHS. Although the NHS is free for the public and anyone in need should have equal access to this, we have evaluated studies which suggest this may not be the case and that further work is required so that we can overcome these disparities.

A limitation of this review article has been that not every available immunotherapeutic agent was reviewed and critically evaluated to discuss the results as well as their impacts on a healthcare system. This review article can be the basis for stipulating further critical reviews of the literature available on all immunotherapies in use or under investigation so that we can further improve the quality of care we provide to patients and suggest methods to make it sustainable within a public health system such as the NHS.

REFERENCES

[1]. Key Statistics for Acute Lymphocytic Leukemia (ALL) [Internet]. www.cancer.org. 2023. Available from: https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/about/key-statistics.html

[2]. Mavers M, Simonetta F, Hidekazu Nishikii, Ribado JV, Maas-Bauer K, Alvarez M, et al. Activation of the DR3-TL1A Axis in Donor Mice Leads to Regulatory T Cell Expansion and Activation With Reduction in Graft-Versus-Host Disease. Frontiers in Immunology. 2019 Jul 17;10.

[3]. Bassan R, Bourquin JP, DeAngelo DJ, et al New approaches to the management of adult acute lymphoblastic leukemia. J Clin Oncol JCO2017773648, 2018.

[4]. Eno J. Immunotherapy Through the Years. Journal of the Advanced Practitioner in Oncology [Internet]. 2017;8(7):747–53. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6188092/#:~:text=The%20first%20immunotherapy%20agent%2C%20an

[5]. Piccaluga PP, Arpinati M, Candoni A, et al. Surface antigens analysis reveals significant expression of candidate targets for immunotherapy in adult acute lymphoid leukemia. Leuk Lymphoma. 2011;52(2):325–327

[6]. Maury S, Chevret S, Thomas X, Heim D, Leguay T, Huguet F, et al. Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia. New England Journal of Medicine. 2016 Sep 15;375(11):1044–53.

[7]. Hoelzer D, Gökbuget N. Chemoimmunotherapy in acute lymphoblastic leukemia. Blood Rev. 2012;26(1):25–32

[8]. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol. 2010;28(24):3880–3889

[9]. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569–1580.

[10]. Saleh MM, et al. (2020). The risk of hypogammaglobulinemia in patients receiving rituximab-based cancer treatments. PLoS ONE, 15(9), e0239351.

[11]. Carson KR, et al. (2009). Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: A report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood, 113(20), 4834-4840.

[12]. Evens AM, et al. (2013). Neutropenia in CD20-targeted therapy for non-Hodgkin lymphomas: Risk factors and management. Leukemia & Lymphoma, 54(5), 971-974.

[13]. Selby P, Kirsty Sharplin, Osborn M, Yeung DT. Management of Philadelphia Chromosome-positive Acute Lymphoblastic Leukaemia. 2023 Jan 1;289–310.

[14]. Salles G, Barrett M, Foà R, Maurer J, O'Brien S, Valente N, et al. Rituximab in B-Cell Hematologic Malignancies: A Review of 20 Years of Clinical Experience. Advances in Therapy [Internet]. 2017;34(10):2232–73. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5656728/

[15]. Martinelli G, Boissel N, Chevallier P, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. J Clin Oncol. 2017;35(16):1795-1802.

[16]. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. New England Journal of Medicine [Internet]. 2017 Mar 2;376(9):836–47. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1609783

[17]. Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE, et al. Tumor antigen–specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood. 2009 Aug 20;114(8):1537–44.

[18]. Salmaninejad A, Khoramshahi V, Azani A, Soltaninejad E, Aslani S, Zamani MR, et al. PD-1 and cancer: molecular mechanisms and polymorphisms. Immunogenetics. 2017 Jun 22;70(2):73–86.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT1931

[19]. Price T, Chawla S, Falchook G, Prenen H, Lugowska I, Subbiah V, et al. 403 Early results from a phase 1 study to evaluate safety, pharmacokinetics, and efficacy of AMG 404, a programmed death-1 (PD-1) antibody, in patients with advanced solid tumors. Journal for ImmunoTherapy of Cancer [Internet]. 2020 Nov 1 [cited 2023 Nov 7];8(Suppl 3). Available from: https://jitc.bmj.com/content/8/Suppl_3/A245.1

[20]. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507–17.

[21]. Turtle CJ, Hanafi L-A, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR–T cells of defined CD4+: CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126:2123–38.

[22]. George S, Bell EJ, Zheng Y, Kim R, White J, Devgan G, et al. The Impact of Adverse Events on Health Care Resource Utilization, Costs, and Mortality Among Patients Treated with Immune Checkpoint Inhibitors. Oncologist [Internet]. 2021 Jul 1 [cited 2022 Mar 26];26(7):e1205–15. Available from: https://eds.p.ebscohost.com/eds/pdfviewer/pdfviewer?vid=7&sid=0a01afa3-4f63-4e21-a7ed-1e5d7579eee5%40redis

[23]. Magee, et al. Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: A systematic review and meta-analysis of randomized clinical trials [Internet]. Elsevier; 2020. Available from: https://www.sciencedirect.com/science/article/pii/S0923753419354638

[24]. CONFIDENTIAL UNTIL PUBLISHED Final appraisal determination -Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (CDF review of TA447) [Internet]. Available from: https://www.nice.org.uk/guidance/ta531/documents/final-appraisal-determination-document#:~:text=The%20average%20cost%20of%20a

[25]. Zhang C, Zhang J, Tan J, Tian P, Li W. Cost-Effectiveness of Pembrolizumab for the treatment of Non–Small-Cell lung cancer: A systematic review. Frontiers in Oncology. 2022 Aug 26;12.

[26]. Information Services Division A National Statistics publication for Scotland Cancer Mortality in Scotland [Internet]. 2019. Available from: https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-10-29/2019-10-29-Cancer-Mortality-Report.pdf

[27]. Bhayat F, Das-Gupta E, Hubbard R. Bone marrow transplantation in AML, and socioeconomic class: a UK population-based cohort study. BMC Cancer. 2010 Sep 28;10(1).