Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Stratification of treatment for adult patients with acute leukaemia

1. Summary of the impact

Research conducted at UCL/UCLH over the last 20 years has enabled the identification of adults with acute leukaemia who are most likely to benefit from the use of stem cell transplantation, i.e. those with acute leukaemia in first remission. The treatment is highly intensive, potentially toxic and expensive high-dose chemotherapy followed by haemopoietic stem cell transplantation, and is inappropriate for some patients. The work has made a major contribution to the development of guidelines worldwide for the treatment of this disease. Improved patient selection for transplantation results in improved survival, less toxicity with improved overall quality of life, and a more appropriate use of NHS resources.

2. Underpinning research

Around 2,500 adults in the UK are diagnosed with acute myeloid and lymphoid leukaemias (AML and ALL) each year. Their treatment includes intensive courses of cytotoxic chemotherapy and consideration of additional high dose cytotoxic therapy and haemopoietic stem cell transplantation (HSCT). Work from UCL has defined those patients with acute leukaemia most appropriately treated with high dose cytotoxic therapy and HSCT.

Acute Myeloid Leukaemia (AML)

Professors Goldstone (UCL) and Burnett (Glasgow, later Cardiff) were asked by the MRC to design and set up national randomised trials addressing the value of both autologous and allogeneic stem cell transplantation in AML. The AML10 trial (1988-1995) recruited 1,571 adult patients and confirmed that high dose therapy and an autologous HSCT resulted in a reduced relapse rate, but no overall reduction in death rate, due to unexpectedly high procedure-related mortality **[1]**. Allogeneic transplantation was shown to be beneficial only in a subset of patients. Further analysis of this latter question in the subsequent MRC AML12 trial (1995-2002) indicated that the greatest benefit was in patients with certain markers of chromosomal damage (cytogenetics) and that allogeneic HSCT could be avoided in subgroups of patients who had very good results with chemotherapy alone. This trial was led by Burnett in Cardiff, and Goldstone contributed to the conception and design of the trial. The cytogenetic risk classification used in both trials was developed at UCL **[2]**. This has since been adopted worldwide and is used to select those patients who get the most benefit from transplantation.

In parallel with the national trials a DNA/RNA/cell bank was established by Professor Linch at UCL and point mutations, insertions and deletions were analysed in selected genes. These landmark biomarker studies from UCL involve the largest cohorts of linked mutation and outcome data in AML worldwide. In 2001, we published the definitive evidence that mutation of the FLT3 gene (FLT-3-ITD), present in approximately a quarter of patients, was a poor prognostic factor **[3]**. In 2008, in an analysis of 1,425 patients, we demonstrated that the combined determination of FLT3-ITD and NPM1 mutation status could be used to further stratify patients into three, therapeutically relevant, prognostic groups **[4]**, thereby further refining the selection of patients for transplantation. Subsequently (2008-13), we have analysed other recurrent gene mutations in AML, refining prognostic stratification and establishing principles of the interpretation of mutation analysis relevant to other forms of cancer. For example, our studies of the CEBPA gene have indicated that biallelic (but not monoallelic) mutations have a sufficiently good prognosis to be spared an allogeneic transplant **[5]**.

Acute Lymphoid Leukaemia (ALL)

In the second major type of acute leukaemia in adults, acute lymphoblastic leukaemia (ALL), Professor Goldstone, with colleagues from the US, set up the MRC ALL12 trial (1993-2004) which explored issues of dose intensification. This trial recruited 1,914 patients, the largest ever in adult ALL, and showed that standard maintenance chemotherapy was preferable to consolidation with high dose therapy and an autologous HSCT, and that an allogeneic HSCT from a matched sibling was the treatment of choice in standard risk patients **[6]**.

3. References to the research

[1] Burnett AK, Goldstone AH, Stevens RM, Hann IM, Rees JK, Gray RG, Wheatley K. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. Lancet. 1998 Mar 7;351(9104):700-8. http://dx.doi.org/10.1016/S0140-6736(97)09214-3

[2] Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, Rees J, Hann I, Stevens R, Burnett A, Goldstone A. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. Blood. 1998 Oct 1;92(7):2322-33. http://bloodjournal.hematologylibrary.org/content/92/7/2322.full.pdf

[3] Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, Walker H, Wheatley K, Bowen DT, Burnett AK, Goldstone AH, Linch DC. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001 Sep 15;98(6):1752-9. http://dx.doi.org/10.1182/blood.V98.6.1752

[4] Gale RE, Green C, Allen C, Mead AJ, Burnett AK, Hills RK, Linch DC; The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008 Mar 1;111(5):2776-84. http://dx.doi.org/10.1182/blood-2007-08-109090

[5] Green CL, Koo KK, Hills RK, Burnett AK, Linch DC, Gale RE. Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. J Clin Oncol. 2010 Jun 1;28(16):2739-47. http://dx.doi.org/10.1200/JCO.2009.26.2501

[6] Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK,Burnett AK, Chopra R, Wiernik PH, Foroni L, Paietta E, Litzow MR, Marks DI, Durrant J, McMillan A, Franklin IM, Luger S, Ciobanu N, Rowe JM. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008 Feb 15;111(4):1827-33. http://dx.doi.org/10.1182/blood-2007-10-116582

4. Details of the impact

The overall impact of this work has been to avoid the unnecessary use of stem cell transplantation in adults with acute leukaemia by identifying those who are most likely to benefit from this procedure.

Impact on guidelines and clinical practice

Following the publication of the results of the AML 10 and 12 trials, jointly devised by researchers at UCL and Glasgow (subsequently Cardiff), the consolidation of first remission AML with an autologous stem cell transplant has ceased in the UK and most other parts of the world. An allogeneic transplant from a matched sibling had been the treatment of choice for consolidation in

first complete remission, but we were able to show that this should not be carried out in patients with good risk cytogenetics, classified according to a system developed at UCL and known as the MRC classification. By a series of sequential biomarker studies carried out at UCL, we have been able to further subdivide patients into specific prognostic categories according to the presence and level of specific mutations. This allows low risk patients to be spared an allogeneic transplant and this risk classification has been incorporated into treatment algorithms throughout the world. Such use of molecular biomarkers is now standard of care in the UK and is used to stratify patients in the current UK AML17 trial **[a]**.

The results of our research underpin European guidance on AML produced by the European Leukaemia Network **[b]**. These guidelines are signposted by the British Committee for Standards in Haematology **[c]**. US National Comprehensive Cancer Network guidelines for the treatment of AML also cite our work **[d]**.

In ALL, the demonstration that autologous transplantation has no role in the management of this disease means that this treatment is no longer used in the UK and further afield. The results of ALL12 are widely cited in justifying treatment recommendations for adult ALL in the US (NCCN) and European (ELNET) guidelines **[e, f]**.

Impact on the health of individuals

By defining the patients most likely to benefit from HSCT, this research has had a significant impact on individual health. For AML, these results have influenced clinical practice in the developed world since approximately 1999 and for ALL since 2004. Importantly, patients *unlikely* to benefit from HSCT can be identified – in adult AML, using the combination of cytogenetic and molecular markers, about 400 patients per year in the UK can be spared consideration of an allogeneic HSCT in first remission (based on UK AML incidence data in under 65 year olds who would be transplant-eligible **[g]** and breakdown of AML into prognostic categories **[h]**.) The equivalent figures per annum for the USA and the European Union (excluding the UK) are 2,000 and 3,000 respectively **[i]**. Avoidance of HSCT reduces the significant risks of treatment-induced toxicity and mortality and improves the quality of life for patients being treated for acute leukaemia.

Economic benefits

An allogeneic transplant from a matched sibling currently costs approximately £70,000 to the NHS and the cost of an autologous transplant is approximately £35,000. In AML, the avoidance of 400 allogeneic HSCT by risk stratification is a potential saving of £28m per annum. Although harder to quantify, avoiding HSCT may have a significant positive impact on the economy more widely, as patients avoid treatment-related mortality and chronic disability which may be associated with HSCT. In ALL, approximately 100 adult patients per year could be treated with an autologous HSCT and the demonstration that this is not necessary by the ALL12 study is a potential saving of £3.5 million per year **[j]**.

5. Sources to corroborate the impact

[a] Documentation regarding the Acute Myeloid Leukaemia clinical trial 17 is available to download from: http://aml17.cardiff.ac.uk/files/files.htm. Including the AML17 Protocol version 8.0 (October 2012), see page 61. http://aml17.cardiff.ac.uk/files/new5/AML%2017%20Protocol%20V8.0%20October%202012.pdf

[b] http://www.leukemia-net.org/content/physicians/recommendations/index_eng.html Döhner H, Estey EH , Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ , Sanz MA, Sierra J, Tallman MS, Löwenberg B and Bloomfield C D. Diagnosis and management of Acute Myeloid Leukemia in adults. Recommendations from an international expert panel, on behalf of European LeukemiaNet. Blood 2010 Jan 21;115(3):453-74.

http://dx.doi.org/10.1182/blood-2009-07-235358. Reference 1 is cited on page 461. Five other papers to which the group have contributed are also referenced.

[c] This is linked to from the British Committee for Standards in Haematology (BCSH) website at: http://www.bcshguidelines.com/353_NON-BCSH_GUIDELINES.html
Although not endorsed by the BCSH, they state that "These Guidelines have not been prepared by BCSH. However, they have been reviewed by the relevant Task Force and deemed appropriate that they are sign posted. The BCSH will not be producing guidelines in these areas."

[d] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Acute Myeloid Leukemia, Version 2.2013, January 2013. http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (login required - copy available on request). The AML 10 trial is cited on page MS-27.

[e] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Acute Lymphoblastic Leukemia, Version 1.2013, March 2013.
http://www.nccn.org/professionals/physician_gls/pdf/all.pdf (login required - copy available on request). Reference 6 is cited on page MS-25.

[f] Gökbuget et al. Recommendations of the European Working Group for Adult ALL. UNI-MED Verlag AG, 2011. Abstract available at http://www.leukemia-net.org/content/leukemias/all/standards_and_sop/index_eng.html

[g] Data on the incidence of leukaemia in the UK can be found at:
http://www.cancerresearchuk.org/cancer-info/cancerstats/types/leukaemia/incidence/

[h] Breakdown of AML into prognostic categories: Patel JP, Levine RL. How do novel molecular genetic markers influence treatment decisions in acute myeloid leukemia? Hematology Am Soc Hematol Educ Program. 2012;2012:28-34.
http://asheducationbook.hematologylibrary.org/content/2012/1/28.long

[i] Data on the incidence of leukaemia in the US and EU were obtained from
http://seer.cancer.gov/faststats/index.php

[j] Based on 2013/14 tariff for Adult Bone Marrow Transplantation. Corroboration available from Head of Contracts (Acute), University College London Hospitals NHS Foundation Trust. Contact details provided.