



TEN YEAR REVIEW

(Abbreviated version)

CUP Foundation – Jo's friends has been in existence for ten years. It was registered as a charity on 24 May 2007. (The charity takes its name from Jo who died from CUP in her mid 40s in 2006). Ten years on and the biology of CUP is no more understood than it was in 2007; yet more has happened to benefit CUP patients in the last ten years than in any previous decade. As a result of developments in cancer research, as well as improved management and treatment, there are grounds for cautious optimism in 2017.

WHERE ARE WE NOW?

CUP is no longer the neglected cancer group that it was ten years ago. The NICE Guideline for England, Wales and Northern Ireland has largely eradicated the nihilistic approach and the sub optimal care that many CUP patients experienced. CUP research is gaining momentum.

Management and treatment

- The NICE Guideline. The most important event for the management and treatment of patients in the last 10 years has been the development and introduction of the NICE Guideline for CUP (for England, Wales & N. Ireland). This has moved NHS treatment for CUP from *ad hoc* to a rational, consistent, evidence-based approach. No longer is CUP a failure of diagnosis: it is a diagnosis in its own right. Now hospital Trusts have local protocols, based on the NICE Guideline, for a CUP Multi-disciplinary Team (MDT) to follow. Admittedly, some Trusts are more compliant than others but the situation overall is vastly improved. The CUP Cancer Nurse Specialist (CNS), of which there were none ten years ago, is part of the MDT and highly valued by the patient.
- Molecular profiling. Molecular profiling, or gene expression profiling, of the tumour goes further than standard immunohistochemistry (IHC) in identifying the most likely primary site from the tissue biopsy. It is not funded on a regular basis by the NHS and it is generally only available to UK patients for a trial, or if paid for privately, or through health insurance (the cost is in the region of £2,000 – £2,500). Molecular profiling has become increasingly sophisticated over the past 10 years but it is not suitable for all patients.

Research

- CUP-ONE. In the UK the only significant clinical research has been *CUP-ONE* led by Dr Harpreet Wasan which has accrued over 600 patients in the past 10 years. The trial is now closed and the results are expected later in 2017. The trial tested a particular chemotherapy combination and, more significantly, a gene expression profiling assay. Pleasingly, research projects are

growing worldwide and outline descriptions of ones from Greece, Italy, France, USA and Australia are shown on our website.

- Patient experience research. Patient experience research is important to improve the management of CUP patients and we have undertaken this, often in conjunction with Southampton University. Combining research findings from Australia and Greece with those undertaken in the UK, in comparing CUP patients with site-specific cancer patients, it is clear that: CUP patients, in comparison with those diagnosed with a known cancer, have a poor quality of life with higher levels of anxiety and depression, and worse physical, emotional, role and cognitive functioning.
- The Hundred Thousand Genomes Project. In December 2012 the British government earmarked £M100 for a '100,000 Genomes Project' and on 5 July 2013 *Genomics England* - a company established by the Department of Health - was launched to deliver the project. Up to 100,000 patients with particularly complex diseases are having their whole genome - their personal DNA code –sequenced. We made representations for the inclusion of CUP and it has been included as one of the diseases to be studied.
- Biomarkers pilot project. We have contributed £55,000 to Dr Wasan at Hammersmith Hospital for a molecular profiling pilot project that aims to uncover potential biomarkers (predictive and prognostic) for CUP. Next generation sequencing (NGS) is being performed on a subset of the samples as a pilot to help understand the disease and detect potentially 'drug-able' mutations. A successful pilot will enable further research.
- Epidemiology - Defining CUP. Accurate measurements of a disease are critical for research funding, international comparison and patient management. Ten years ago CUP was known by a number of different and confusing descriptors. We have encouraged the single descriptor of 'Cancer of Unknown Primary' and a clear delineation of what international classification codes constitute CUP. Before CUP was defined, in the NICE Guideline, it was easier to dismiss the condition on the basis of its heterogeneity. We can now make some interesting comparisons. For example, in the 20 years from 1993 to 2013 there was a decline in UK CUP incidence of 37% and a decline in mortality of 28%. We initiated and have undertaken research, with international partners, looking at international comparisons. Our study exposed the differences in registration and reporting practices for CUP in Australia, England, Wales, Scotland, N. Ireland, and the Republic of Ireland.

The size and shape of the problem in the UK in 2017

- CUP is the 11th commonest cancer in the UK (13th in men, 8th in women). CUP represents about 3% of all cancer incidence.
- Nearly 30 people in the UK die each day from CUP (about 6% of all cancer deaths). CUP is the 5th highest cause of cancer death in the UK (after lung, bowel, breast and prostate cancers).
- 57% of patients diagnosed with CUP in the UK present as an emergency, compared with 23% for 'all cancers'.
- 55% of CUP cases occur in those aged 75 and over.
- 21% of CUP patients are in the most deprived socio-economic group.
- In the last decade CUP incidence has declined by 28% and mortality by 24%. (The previous decade saw a decline of only 9% and 4% respectively).

Data sources: CRUK, NCIN now NCRAS.
Incidence and mortality data are from 2014

Conferences and workshops

It is through clinicians and scientists sharing knowledge and best practice that patients will benefit from research and improved management. In 2009, 2012 and 2015 we ran major international conferences in London bringing together clinicians and scientists to share the latest research. Up to that point, no other international conferences had been held devoted to CUP. We were fortunate to have the leading authority on CUP, Dr Tony Greco (USA), chair the conferences. We ran also, with the support of the European Society of Oncologists, an event in London chaired by Professor Nicholas Pavlides for junior oncologists. Training for UK CUP MDTs has taken place in association with *SBK Healthcare*. We attend and present papers at many conferences.

Awareness

Awareness of CUP (and the charity) amongst treating physicians has now reached high levels. Many oncologists and Cancer Nurse Specialists (CNSs) pass on details of our website to patients. We have contributed a number of articles to medical journals about CUP and given interviews on radio (national and local) and TV both in the UK and in the USA. Our fundraisers are our principal public awareness-raisers. The many and varied activities they undertake lead to articles in the local press. On the whole, however, the general public's awareness of CUP remains very limited. This adds to the distress of patients because it is frustrating to have to explain the unique nature of a CUP diagnosis to friends and acquaintances.

Information and support

Providing information and support to patients and their families is at the heart of our work. Registered in England and Wales we have a worldwide reach as the only substantive charity focused on CUP. Our website has some 1500 hits per month from all over the world. We reach the widest audience through the internet and we receive also many individual requests by eMail. We have produced a hard copy booklet in conjunction with *Cancer Backup* – a charity which has now been absorbed by *Macmillan Cancer Support*. The booklet 'Understanding Cancer of Unknown Primary' is distributed by *Macmillan* and we are invited to contribute to every update.

Examples of our work

- Information and support for CUP patients and their families. Our website has some 1500 hits per month. Registered in England and Wales we have a worldwide reach as the only substantive charity focused on CUP.
- Advocacy. We are the 'go to' charity for pharma, government, researchers, and clinicians seeking information about CUP patients, diagnosis and treatment. As patient advocates we have been involved in the NICE Guideline and Peer Review Measures development as well as clinical research such as CUP –ONE.
- Knowledge-sharing. We have gathered world experts to attend our international conferences; held training events for oncologists; and participated in CUP MDT development days.
- Raising awareness. We have raised awareness of CUP amongst the UK medical profession and major cancer charities. Our supporters raise public awareness through local fund-raising events.
- Research funding. We have funded patient experience research, to understand better the needs of CUP patients, as well as clinical research.

WHAT OF THE FUTURE?

The author William Gibson was not, but could have been, writing about CUP with his contention that: “The future is already here – it's just not evenly distributed”.

The future for CUP patients – and it is partly here, but not evenly distributed - lies in understanding the molecular nature of the cancer. Two ways of approaching this are apparent: using gene expression profiling of the CUP tumour to aid diagnosis which gives a better idea of its primary site for chemotherapy treatment; and using Next Generation Sequencing of biopsied tissue to identify ‘actionable mutations’ of the cancer, for targeted treatments (immunotherapy), where the primary site is of little relevance.

At our 2015 international conference, Dr Tony Greco of *The Sarah Cannon Cancer Center* in the USA, who was chairing the conference took our charity strapline of ‘making the unknown, known’ and stated that the unknown is now known. Dr Greco’s view is that about 95% of Cancers of Unknown Primary can be identified through a combination of IHC and molecular profiling. This focuses treatment more accurately but for a late stage metastatic cancer patient there may only be marginal impact on life extension for the patient.

We continue to argue that palliative care support should be available at the start of the patient pathway and we are working with experts to define a Patient Decision Aid (PDA) for CUP. A PDA can help patients and families understand the treatment options in the patient pathway.

In terms of a future treatment, which has the potential to offer better outcomes for CUP patients, immunotherapy offers exciting, but untried, possibilities. Immunotherapy treatment has led to remarkable clinical responses in patients with many different types of ‘hyper-mutated’ cancers, including melanomas, non–small-cell lung cancer, renal cell carcinoma, bladder cancer, and Hodgkin’s lymphoma. Research is needed to look at immunotherapy in relation to CUP and we have committed £100,000 to help initiate a trial at Hammersmith Hospital.

The full version of this paper is available on our website
www.cupfoundjo.org