MEDICAL ONCOLOGY GROUP OF AUSTRALIA INCORPORATED

A.B.N 94 601 175 669

Wednesday 28 February 2018

Mr Simon Shinkfield
Coroner's Registrar
65 Kavanagh Street
Southbank 3006
Melbourne, Victoria
cpuresponses@coronerscourt.vic.gov.au

Dear Mr Shinkfield

RE: Investigation into the death of Graeme H Griffiths Court Ref: COR 2015 004937

I am responding to your letter of 29 November 2017 requesting advice from the Medical Oncology Group of Australia (MOGA). The Association is the national professional organisation for Australian medical oncologists and a Speciality Society of the Royal Australasian College of Physicians.

The Association maintains a strong advocacy position that supports international, best clinical practice at all times including the best available standard of care for all our patients.

5-Fluorouracil (5FU) is a fluorinated pyrimidine analogue commonly used in combination chemotherapy regimens for patients with breast, colorectal, lung cancers, and other malignancies. Dihydropyrimidine dehydrogenase (DPD), an enzyme encoded by the DPYD gene, is the rate-limiting step in pyrimidine catabolism and deactivates more than 80% of standard doses of 5FU and the oral 5FU prodrug capecitabine. DPD deficiency affects approximately 5% of the overall population. In these patients, the lack of enzymatic activity increases the half-life of the drug, resulting in excess drug accumulation and toxicity. Additionally, 3%-5% of the population has a partial DPD deficiency due to sequence variations in DPYD gene, which potentially limits their ability to fully metabolise the drug, thereby resulting in toxicity.

Increased susceptibility to 5-fluorouracil (5-FU)/capecitabine can lead to rapidly occurring toxicity (which may be life-threatening) caused by impaired clearance resulting from dihydropyrimidine dehydrogenase deficiency, and other genetic variations in the enzymes that metabolize 5-FU. In addition, life-threatening 5-FU toxicity can occur because of overdoses due to infusion pump errors, dosage miscalculations, and accidental or suicidal ingestion of capecitabine. Uridine triacetate (Vistogard) was approved by the US FDA in 2015 for adult and paediatric patients who exhibit early-onset severe or life-threatening 5-FU/capecitabine toxicities or present with an overdose. Uridine triacetate delivers high concentrations of uridine, which compete with toxic 5-FU metabolites. In two open–label clinical studies, uridine triacetate was shown to be a safe and effective lifesaving antidote for capecitabine and 5-FU overexposure, and facilitated the rapid resumption of chemotherapy.[1]

Access to uridine triacetate (Vistogard) is already supported by eviQ but currently there is no Australian supplier for uridine triacetate (Vistogard) and the impacts of this situation were detailed in a conference presentation in November 2016, as follows, "This case highlights the difficulty in timely access of this lifesaving medication for Australian patients."[2]

Therefore, The Association supports the recommendation that there be a co-ordinated response at both the Federal and State levels to establish a single national repository for the supply and distribution of Vistogard in Australia. The Association also supports the recommendation that the Peter MacCallum Cancer Centre in Melbourne is a suitable facility to act as the national repository for the supply and distribution of Vistogard in Australia as well as manage the establishment of National supply and distribution arrangements. The Association has previously written to Wellstadt on two occasions to articulate the latter recommendation. The issue of cost to enable access to Vistogard on a national level needs to aslo be considered, as Vistogard is not funded through the Public Benefits Schedule (PBS).

In response to your request for the Association to consider and comment on whether DPD testing should be standard care for all patients before starting fluoropyrimidine chemotherapy, we present the following advice;

Multiparametric testing (both genotyping and measures of metabolites) has been used in Europe. In an experience of over 1000 patients this modestly reduced the incidence of severe side effects in the group tested: severe side

effects were seen in 10% of patients that we screened for DPD enzyme deficiency with no deaths compared with severe side effects observed in 17% of patients that were untested for DPD deficiency and this group had an 0.25% death rate (published in Seminars Oncology 2017).[3]

This testing was effective in a health care system that included the following parameters:

1. Rapid turn-around so institution of therapy is not delayed[10 days in France]
2. Universal access (available to all oncologists in France, specific system set up for transport of specimens to a central laboratory)
3. The €190 cost was covered by the French health system.

Until a similar system exists in Australia the medical oncology profession cannot recommend this as a standard of care. It is also unclear whether this would be cost effective in the Australian health system. We would suggest that such a testing system be investigated by the Medical Services Advisory Committee and, if found to be cost effective, that the necessary infrastructure be funded and the test be adequately rebated to make this available to all patients.

DPD Testing is currently not the standard of care for patients before starting fluoropyrimidine chemotherapy. Australian medical oncologists do not generally use or recommend DPD testing and the test is not included on the Australian Medical Benefits Schedule and, is therefore not rebated. DPD testing is not recommended by eviQ, the NSW government online resource for cancer treatment protocols developed by multidisciplinary teams of cancer specialists; https://www.eviq.org.au/about-us.

The explanations for this position relate to major practical barriers that preclude routine DPD testing in Australia (and other localities around the world), including [4]:

- Genetic testing is difficult to interpret and is not necessarily reflective of enzymatic deficiency nor are genetic abnormalities when identified necessarily predictive of all cases of life-threatening toxicity;
- The impact for subsequent treatment (should an abnormal genetic test be identified), is not clear cut;
- Enzymatic testing is currently difficult to access for some oncologists;

- The testing process is slow (current turn-around time is approximately 2 weeks) to the extent that it could significantly compromise outcomes by causing substantive delays in timely institution of therapy;
- The test is relatively expensive (approximately $200) and is not rebated, meaning that the patient will need to bear this expense in most instances; and
- Given the points noted above the test may not be cost effective.

It is also important to emphasise that severe gastrointestinal toxicity may occur in patients without DPD deficiency.

In view of these observations, the GI Expert Committee convened by MOGA is of the view that mandated testing of DPD for all patients prior to fluoropyrimidine chemotherapy administration cannot be currently recommended as routine care.

Medical oncology is a speciality that is characterised by the rapidly evolving and changing nature of our clinical practice, in response to emerging advances in the sciences, research and technology. Accordingly, if DPD testing in the future were to become more rapidly accessible and available, as well as cost-effective, the profession would reconsider the routine applicability of DPD testing in clinical practice. At this time the Association recommends and promotes ongoing education around the use of fluoropyrimidines (fluorouracil and capecitabine), including the monitoring and management of toxicity in clinical practice.

The Medical Oncology Group of Australia trusts this advice will be of assistance. Please do not hesitate to contact the Association if we can provide further assistance.

Yours Sincerely,

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REFERENCES:

1. Muhammad Wasif Saif, Bassel F. El-Rayes, Marwan G. Fakih, Thomas H. Cartwright, James A. Posey, Thomas R. King, Reid W. von Borstel and Michael K. Bamat, Emergency Use of Uridine Triacetate for the Prevention and Treatment of Life-Threatening 5-Fluorouracil and Capecitabine Toxicity, Wen Wee Ma; Cancer 2017;123:345-56.

2. Louisa L Lo , Senthil Lingaratnam, Catherine Rowe, Kelly-Anne Phillips, Poster Presentation Joint 2016 COSA and ANZBCTG Annual Scientific Meeting, An Australian experience of the use of Uridine Triacetate (Vistogard®) antidote for severe capecitabine toxicity- A Case Report (#239) Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.

3. Marie-Christine Etienne-Grimaldi, Chantal Barin Le Guellec , Jean-Christophe Boyer , Etienne Chatelut , Alexandre Evrard , Marie-Anne Loriot , Angelo Paci , Bernard Royer, Fabienne Thomas, Joseph Ciccolini, Prevention of 5-Fluorouracil-Induced Early Severe Toxicity by Pre-Therapeutic Dihydropyrimidine Dehydrogenase Deficiency Screening: The Multiparametric Approach Is Not Convincing, Semin Oncol 44 (2), 159-160. 2017 Jul 04.

4. https://www.rcpa.edu.au/Library/Practising-Pathology/RCPA-Genetic-Testing/rgtl/Items/GeneDetail?symbol=DPYD: https://www.sonichealthcare.com/services/laboratory-medicine-pathology/australia/