Supplementary Submission No 95a

INQUIRY INTO OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NSW

Name: Dr Laurence J Denholm

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NSW LEGISLATIVE COUNCIL SELECT COMMITTEE ON OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NEW SOUTH WALES - Additional comments.

1. Tumour HPV status is important in analysis of the SVH patient dataset.

Recognition that specific oncogenic strains of the Human Papilloma Virus (HPV) are a common cause of head and neck squamous cell carcinoma (HNSCC) and the increasing proportion of HNSCC tumours, particularly oropharyngeal carcinomas (OPC), that are HPV positive has been a major issue in head and neck cancer globally in recent years - described as a HPV "epidemic".[1] The HPV status of a HNSCC is significant because:

(i) There is potential for radiation dose de-escalation without reducing long-term survival, thereby reducing later radiation toxicity. (HPV positive HNSCCs are more radiosensitive than smoking and alcohol related HPV negative HNSCCs.);

(ii) The prognosis for HPV positive HNSCC is much better than that for HPV negative HNSCC, with a 58% reduction in the risk of death[2]; and

(iii) The ratio of HPV positive to HPV negative tumours in a HNSCC patient group has a significant impact on the expected overall survival rate for the group.

Several large multi-centre trials of treatment de-intensification in HPV positive HNSCC are in progress overseas and in Australia, with completion dates from 2016 to 2021.[1]

As survival is significantly better for patients with HPV positive OPC than patients with HPV negative OPC (82% vs 57% at 3 years[2]), if tumour tissue or histological sections are still available, future analysis of the SVH patient dataset could be improved by determining the HPV status of the 86 patients currently without HPV status data, using *in situ* DNA hybridisation for oncogenic HPV strains and P16 immunochemistry.

Forty (65%) of the 62 SVH low dose carboplatin patients with known tumour HPV status were HPV positive. HPV status is sufficiently significant for authorities to argue that patients with HPV positive and HPV negative tumours should be distinguished and analysed as separate cohorts. The Currow report did not do this and it is not yet clear whether or not HPV status can be identified as a factor affecting clinical outcomes for 100 mg flat dose carboplatin treated patients. It is possible that the radiosensitising efficacy of low dose carboplatin is different in HPV positive and HPV negative tumours.

2. Knowledge of variation in radiation dose may be important in determining the impact of variation in carboplatin dose in the SVH patient dataset

In concurrent chemoradiotherapy for HNSCC, tumour progression and patient survival are affected by radiation dose and fractionation, with potentially greater impact on survival from radiation dose variation than chemotherapy dose variation. It may be difficult to separate any impact on tumour progression and patient survival in the SVH dataset from low dose carboplatin treatment from the impact of radiation dose variation, if there was significant variation in the radiation dose of these patients.

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[1] Lewis *et al* (2015) "The New Face of Head and Neck Cancer: The HPV Epidemic" Oncology Journal 29(9) 616-626 (Online at http://www.cancernetwork.com/oncology-journal/new-face-head-and-neck-cancer-hpv-epidemic)

[2] Ang *et al* (2010) Human papilloma virus and survival of patients with oropharyngeal cancer N Engl J Med 363(1):24-35

Although the Currow report indicates that radiotherapy data was collected for most of these patients[3], it does not say whether there was any correlation between the radiation dose and the chemotherapy dose of individual patients. Nor does the report disclose the range of radiation doses in these SVH patients. Given the increasing incidence of HPV positive HNSCC and the trend to dose de-escalation in such patients, it is likely there was some significant variation in radiation dose of the SVH patients. In the case I am familiar with, the radiation dose was reduced to avoid future radiotoxicity, specifically because the tumour was HPV positive, but the platin dose was not reduced. If there is an observed increase in cancer recurrence or mortality in the SVH flat 100 mg carboplatin patients, it will be important to distinguish any effect of variation in radiation dose from any effect of variation in chemotherapy dose.

3. Ongoing analysis of the SVH dataset is important to patients and families

The most important question in the minds of patients and their families since this off-protocol chemotherapy prescribing issue emerged in the media is really quite simple. "Did concurrent radiochemotherapy with a flat 100 mg initial dose of carboplatin harm patients by increasing their risk of tumour progression and death?" This is not a question that will go away. Regular monitoring of the surviving patients in the SVH patient dataset, with transparent disclosure of the monitoring and data analysis methodologies and the results, will remain a matter of critical interest to surviving patients and families until this question is answered. Clear communication to patients and families about future monitoring of affected patients and their pair matched controls, the data analysis methodology and how results will be disclosed is critical.

If the SVH dataset does not have sufficient power to detect the maximum variation in tumour progression and survival that could be expected (ie the variation expected if no chemotherapy was provided), then patients and families should be advised of this forthwith, rather than left waiting for an anticipated answer. It should however be made clear that any failure of the dataset to demonstrate an effect of the 100 mg flat dose carboplatin protocol on survival cannot be used to infer there was no such effect.

Current data analysis comparing low carboplatin patients with matched patients from two other SVH cohorts[3] should be supplemented by comparison against published progression and survival data from HNSCC patients elsewhere. If SVH patients are different to patients elsewhere (for example, in comorbidity rates), then the evidence for these differences should be disclosed together with estimated survival rates. Estimated survival should allow for the proportion of HPV positive cases.

Clear statements about this monitoring program are particularly important now that the s.122 Inquiry is finished and the expert panel has disbanded. Patients and families may well understand that the SVH patient dataset is not able to provide the answer to their key question about harm to patients in 2016, but they would like to know if and when the dataset is expected to be able to answer this question. Some public statement on the power of the dataset to identify variations in patient outcomes with flat 100 mg dose carboplatin treatment would be useful.

[3] Currow D et al (2016) Inquiry under section 122 of the Health Services Act 1997: Off-protocol prescribing of chemotherapy for head and neck cancers. Final report 31 July 2016, Appendix B. At http://www.health.nsw.gov.au/patients/cancertreatment/Documents/section-122-final-report.pdf

Patients and families must have confidence that a rigorous, ongoing, comprehensive and **independent** process of patient monitoring and data analysis is being pursued. They need to know who is responsible and that those responsible have no conflicts of interests. Patients and families also need to know how the results will be disclosed in a timely manner. In the circumstances, this is not an unreasonable expectation.

There is lack of transparency in the published data to date. For example, there is a useful chart in Appendix B of the Currow Inquiry report with data on clinical outcomes for the 103 patients in the 100 mg flat dose carboplatin cohort, but the value of this data for the reader is greatly diminished because the chart does not provide the same clinical outcomes data for patients in the two comparative groups that are to be used for the pairwise analysis - the 54 patients in the >100 mg carboplatin cohort and the 38 patients in the cisplatin cohort. This missing data reduces the value of the data that is published.

4. Off-protocol prescribing is not bad *per se.*

Appropriate off-protocol prescribing for individualised treatment and off-protocol prescribing which implements a new standard protocol without proper supporting scientific evidence must be distinguished.

Where a clinician is prescribing off-protocol for a small proportion of his or her patients, it is likely the purpose of this off-protocol prescribing is individualised treatment according to the individual patient's needs and wishes. Where a clinician is prescribing off-protocol for the majority of his or her patients (and particularly if the off-protocol dose is identical for all these patients despite significant clinical differences between them), then it is likely this off-protocol prescribing reflects the adoption of a new standard protocol by that particular clinician. If this new standard protocol is unsupported by any research evidence and outside normal prescribing guidelines, then its adoption must be considered experimental. Repeated use of the same unproven protocol without appropriate individual patient clinical justification in each case suggests an informal clinical trial.

If off-protocol prescribing is based on individual patient needs, the reasons for dose variation should be documented and the medical oncologist's decision should be subject to a properly documented review by the multidisciplinary cancer team, simply because this decision will often have spillover effects for other clinicians treating the patient, particularly the radiation oncologist, as well as nursing and support staff.

In the context of this Inquiry, the objective of prescribing reform should not be to limit the medical oncologists' discretion in off-protocol prescribing by introducing computer restricted prescribing controls. That is not in the interests of patients. The aim of reform should be to ensure proper documentation and monitoring of any deviation from recommended prescribing guidelines and a multidisciplinary review of all such decisions to deviate to ensure that the clinical justification for variation is appropriate in each case and that other staff treating the same patient are aware of the dose variation and likely impacts for their own clinical or support responsibilities.

Some sections of the oncology community are publicly opposing further restrictions on their prescribing discretion, alleging patients will be harmed by the proposed changes. This would only be true if oncologists elect to use recommended guideline protocols rather than go through the bureaucratic procedures necessary to obtain approval for off-protocol prescribing. With respect to this "red tape", the legitimate requirements of medical oncologists for discretionary off-protocol prescribing to allow individualised patient treatment must be balanced against the community's need to have confidence that no individual oncologist can adopt an unproven protocol as a standard in a way that is outside the boundaries of accepted medical practice.

This is really no different to the current system where medical practitioners require approval from an external authority to prescribe certain drugs for which controlled use is deemed to be in the community interest (for example, some antimicrobials). Practitioners are not prevented from using the specified restricted drugs or restricted dose regimen, but the approval process ensures that these are monitored.

5. Improving Cancer Patient Advisor-Advocacy Services

Several books and numerous medical journal papers describe problems of poor communication and coordination between medical discipline specialists in cancer care. Multidisciplinary teams and "grand rounds" are important strategies to minimise the problems in treatment planning and monitoring but may not address the day-to-day issues for patients. For any patient, the MDT is a daunting environment in which to question a treatment decision or raise concern about supportive care.

Cancer patients are often very sick, particularly towards the end of their primary treatment, and often confused by the organisational complexity of the modern hospital system. Conflicting information from different specialists is, without explanation, particularly corrosive to patient confidence. For the patient, the weeks after cancer diagnosis are like "riding the tiger in a whirlwind". Individual case coordinators are useful to ensure that patients are in the right place at the right time, but they are not advisors or advocates for the patient. They are hospital employees.

Most patients need an independent, informed advisor/advocate/facilitator. This can be a relative or friend, but many patients are alone or have supporters without the capacity to effectively advise and advocate on their behalf. In the context of systemic problems in SVH Cancer Services in 2015, I found this advisory-advocacy role to be challenging, despite my medical background. When I asked reasonable questions I was sometimes faced with resentment and even outright anger on one occasion. The average person could not begin to understand what was going on in this situation or how to frame the right questions to protect the interests of the patient. I managed to work through the failing SVH system to get the correct treatment, but the Currow Inquiry report suggests many people would not have been able to do this.

Effective independent advice and advocacy is most important to the patient when the system is failing them - as it clearly was at St Vincent's Hospital Cancer Services over the last few years. St Vincent's has publicly acknowledged this failure.

There were many wonderful, skilled, ethical and caring people working at St Vincent's Hospital when this crisis occurred. Not just a few, but the majority. And yet the problem did occur.

Concerns expressed by junior staff were ignored, the interests of patients were ignored, mandatory reporting rules were ignored and ultimately there appears to have been an attempt at cover-up whilst correcting the situation, to avoid reputational damage. Failure to disclose as required must be considered a constructive cover-up if proper corrective responses are to be implemented. It is critical to recognise that a decade of off-protocol chemotherapy prescribing was not the real problem, just a symptom of the problem. Off-protocol chemotherapy just happened to be the vehicle by which an underlying problem was revealed, but it might have occurred elsewhere.

The real problem, as Prof. Currow recognised, was an organisational culture problem where senior executives and clinical managers failed to establish the right "tone at the top" and failed to drive the appropriate culture down through their organisation. Poor corporate culture is well recognized as a driver of misconduct that leads to poor outcomes for consumers.[4] In the business world, Board Directors and CEOs are increasingly likely to be held to account for poor organisational culture.

Rigid and formal hierarchical organisational structures where status depends on position, and status is critical to financial success, facilitate a culture in which any question is a challenge to authority and any challenge is a personal threat. But long-standing organisational culture problems cannot be resolved simply by more externally imposed rules. Some external compliance monitoring is also needed. But most of all there must be changes at the top to drive down a more inclusive culture.

This situation at SVH is not unique. A similar situation existed in mental health institutions at the time the Official Visitor program began. Official Visitors are one method for increasing the consideration given to consumer interests, but more will likely be required to avoid a repeat of the SVH Cancer Services failure.

This Parliamentary Select Committee should perhaps give some thought to the introduction of a formal system of independent patient advisor-advocates at NSW hospitals. These people would need to be appointed by an agency outside the hospital system, appropriately qualified and properly resourced. Courage would be a prerequisite. They would need appropriate legal status and powers, including access and inquiry powers within the hospital equivalent to those of Official Visitors. They would have a broad oversight role but only as necessary to inform their advisory and advocacy roles on behalf of patients. Advocacy would be limited to the patients of the hospital and they would be bound not to advocate for any individual patient or group of patients in the media or anywhere outside the hospital.

Each hospital would require at least one standing patient advisor-advocate, but that person should be able to call in additional patient advisor-advocates for a period if there is evidence of systems failure or significant culture problems at the hospital.

[4] Medcraft G. (2016) "Corporate culture, corporate values and ethics" *An edited version of ASIC Chairman, Greg Medcraft's speech at the launch of the Inaugural Governance Institute Ethics Index* at http://asic.gov.au/regulatory-resources/corporate-governance/corporate-governance-articles/corporate-culture-corporate-values-and-ethics/

Most importantly, the patient advisor-advocate would establish a secure system in the hospital for any patient or staff member to disclose their concern about the treatment of a particular patient to the advisor-advocate on a confidential basis. The advisor-advocate would be a local patient ombudsman. Partial cost-recovery could be applied to avoid overuse of the service, but the advisor-advocates should have authority to approach any patient thought to be at risk and offer the service free of charge.

Patient advisor-advocates could play a significant role in ensuring proper informed consent, as they would be completely independent of the hospital in which they were located, independent of the Area Health Service and acting for the patient with the patient's agreement. Precautions would be needed to avoid regulatory capture.

Most importantly, from a consumer perspective, patient advisor-advocates would potentially reduce the information asymmetry and power imbalance inherent in the fiduciary doctor-patient relationship of specialist cancer services. Privacy would of course be a consideration in developing any system of patient advisor-advocates.

The creation of a *NSW Hospital Patient Advisor-Advocate Service*, completely independent of hospital management and Local Area Health Services, but with staff embedded at each hospital location and invested with appropriate powers, would significantly improve public confidence in the system.

6. Follow-up monitoring by medical oncologists after completion of chemotherapy

Completion of oncology treatment as an out-patient or upon discharge from hospital should not end the medical oncologist's responsibility for the patient. On completion of chemotherapy, patients can be quite ill, but even more importantly, these patients can develop serious but delayed side-effects of chemotherapy that are not evident at completion of their treatment. Proper liaison between the medical oncologist and the patient's general practitioner is critical, but this liaison is sufficiently problematic to be the subject of academic research and discussion. GPs may not have good knowledge of the side-effects of particular drugs and should be specifically advised by the treating oncologist. A plan for patient monitoring between completion of chemotherapy and the next consultation with a specialist at the hospital is critical. In the case that I am familiar with, this process failed. Once chemotherapy was completed, there was no further contact with the medical oncologist and responsibility for future monitoring passed back to the surgeon who had limited knowledge of medical oncology. There was no apparent plan for monitoring over the three months between completion of primary treatment and the next scheduled routine consultation with the surgeon.

Potential life-threatening side-effects of chemotherapy may develop in the period between completion of treatment and the next visit to the hospital, such as cardiac arrest from untreated hypokalemia or serious systemic infection from neutropenia or agranulocytosis.

Many authorities consider that proper monitoring of patients in the community after chemotherapy is very important, but it seems not to be uniform across NSW hospitals.