

**A themed review of patient safety incidents
involving anti-cancer medicines
1 November 2003 – 30 June 2008**

October 2010

Full Report

Acknowledgements

This report was produced by the Patient Safety Cancer and Safe Medication Practice teams of the National Patient Safety Agency (NPSA)

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1. Introduction

The National Reporting and Learning System (NRLS) was established in 2003. The system enables patient safety incident reports from the National Health Service to be submitted to a national database. This data is then analysed to identify hazards, risks and opportunities to improve the safety of patient care. Since the NRLS was established, over four million incident reports have been submitted by healthcare staff.

The NRLS is a pioneer and is the most comprehensive of its kind in the world. It uniquely provides the NHS with a national perspective on risks and hazards. This information is used to develop tools and guidance to help improve patient safety at a local level. Most incidents are submitted to the NRLS electronically from risk management systems in local NHS organisations.

The analysis of patient safety incidents involving anti-cancer medicines reported to the National Patient Safety Agency (NPSA) via the NRLS was commissioned as part of a wider programme of work to improve patient safety in cancer in 2008. A review of patient safety incident reports involving anti-cancer agents (see search terms in section 7) between 1 November 2003 and 30 June 2008 was undertaken.

The term 'anti-cancer medicines' has been used throughout to encompass conventional cytotoxic and cytostatic medicines, as well as newer biological treatments such as monoclonal antibodies, so-called 'small molecules', and other targeted therapies.

2. Quantitative Analysis

2.1 Method

A total of nearly 219,000 patient safety incident reports relating to medication were received by the NRLS from NHS staff in England and Wales between 1 November 2003 and 30 June 2008. From these, 4,829 reports (2 per cent) involving anti-cancer medicines were identified for further review. All incidents with a reported outcome of patient death, severe harm or moderate harm were validated by two reviewers. Where the reported outcome of the incident could not be validated, these reports were allocated an outcome of low harm or no harm. There were seven validated incident reports of patient death, nine validated cases of serious harm and nine validated incidents reports of moderate harm. One incident report of severe harm and one of moderate harm were amended to patient death, and one report of moderate harm was amended to severe harm (See Table 1).

A further 1,157 incident reports involving non-cancer methotrexate therapy were identified. These reports usually involved the use of methotrexate as an immunosuppressant to treat a range of non-cancer clinical indications.

2.2 Analysis by clinical outcome

A summary of the analysis of patient safety incident reports by clinical outcome is shown in Table 1. The majority of incidents, 94 per cent (4557) for anti-cancer medicines were associated with low harm or no harm to patients. However, within this group there were many events that could have resulted in much greater patient harm had they not been identified by staff prior to the patient receiving medicines.

Of the remaining 6 per cent (273) of reports which were initially reported as causing moderate, severe harm and death, the number that were independently validated as correct were less than 0.5 per cent of all reports (25).

Table 1. Anti-cancer medicine incidents by clinical outcome

Clinical outcome	Validated incident	Unvalidated
Death	7	9
Severe harm	9	44
Moderate harm	9	220
Low harm	N/A	755
No harm	N/A	3801
Total	25	4,829

2.3 Analysis by stage of the medicine use process

A summary of the analysis of patient incident reports by stage of medicine use process is shown in Table 2. Incident reports involving errors in the administration of anti-cancer medicines were the largest category when analysed by medicine use process (43 per cent), and those involving monitoring of anti-cancer medicines were the smallest number of reports (2 per cent). There were, however, deaths or severe harm incidents associated with all stages of the medicines use process.

Table 2. Anti-cancer medicines incidents by stage of medicine use process

Stage of process	Original reports	% of total	Death	Severe harm	Moderate harm	Low harm	No harm
Prescribing	1,139	23.5	2	3	3	97	1034
Preparation	1,281	26.6	1			146	1,134
Administration	2,080	43.1	1	6	4	500	1,569
Monitoring	115	2.3	3		2	21	89
Other	214	4.5	0			48	166
Total	4,829	100.0	7	9	9	812	3,992

2.4 Analysis by type of medication incident

A summary of the analysis of patient incident reports by type of medication incident is shown in Table 3. The greatest number of incident reports and those associated with most harm, arose from wrong dose, strength, frequency and quantity of anti-cancer medicine.

Wrong medicine, adverse medicine reactions and allergy, accounted for large numbers of incident reports and some deaths and severe harm. There were a large number of reports concerning accidentally delayed or omitted anti-cancer medicines. There were no reports of death, or severe or moderate harm arising from this type of incident, however, it can be difficult to determine the clinical impact of delayed or omitted medicine.

'Others' include wrong formulation, contraindication, and wrong route, where each section comprised <1 per cent of total reports and contained no validated death, severe or moderate reports of patient harm.

Table 3. Anti-cancer medicines incidents by incident type (validated data)

Stage of medication process	All reports	%	Death	Severe	Moderate	Sub-Total
Wrong/unclear dose, strength, frequency, or quantity	1,569	32.5	4	5	2	11
Omitted/delayed medicine	784	16.2	0	0	0	0
Wrong medicine	309	6.4	0	2	1	3
ADR/Patient Allergic	369	7.6	3	2	3	8
Wrong expiry date	232	4.8	0	0	0	0
Wrong medicine label	183	3.8	0	0	0	0
Wrong storage	166	3.4	0	0	0	0
Wrong method of preparation/supply and mismatching between patient and medication	201	4.2	0	0	0	0
Others and Unknown	1016	21	0	0	3	3
Total	4,829	100	7	9	9	25

2.5 Analysis by anti-cancer medicine

A summary of the analysis of patient incident reports by anti-cancer medicine is shown in Table 4. The taxanes, docetaxel and paclitaxel were the most frequently reported group of anti-cancer medicines identified in the patient safety incident reports. Adverse medicine reactions and allergy outcomes (28 per cent) were the most numerous types of reported incidents. It is recognised that adverse events associated with taxanes may, in large part, be due to the solvents in which the medicines are dissolved. Individual examination of many of the incidents labelled as ADR (adverse drug reaction)/Allergic reaction, revealed many reports of extravasation and commonly encountered adverse events that resulted in no harm. Cisplatin was the most frequently reported medicine, with dosing/frequency errors accounting for 30 per cent of the incidents.

Wrong or unclear dose, frequency and quantity accounted for the most numerous types of incidents across nearly all anti-cancer medicines groups. For bortezomib, mitomycin and rituximab, the most common incident reported was 'omitted medicine'. The exact reason was unclear, except for mitomycin when it was as a topical instillation following bladder surgery for malignancy. In these cases, poor communication between pharmacy, wards and operating theatres appeared to be the cause for many of the delayed or missed doses. Dosing errors with capecitabine accounted for over half (55 per cent) of the 368 incidents reviewed for this anti-cancer medicine.

The 'other and unknown' category contained many patient safety incidents (1016) that reporters had simply failed to categorise. Each record was reviewed individually to ensure that no significant reports were overlooked. The vast majority of these reports merely reflected themes that were already identified and resulted in low/no harm to patients. Some specific incidents have been used to highlight trends within the qualitative data section.

It should also be noted that because of the form in which data is received from organisations, the rows and columns in Table 4 may not add up to 100 per cent. The submitted information for an individual error often contains additional information regarding medicines other than those directly involved in the error. Typically, the narrative may mention the names of all the anti-cancer medicine medicines in a protocol, irrespective of whether the incident related to only one or more individual medicines.

Many anti-cancer medicine protocols mentioned in the report are routinely referred to by abbreviations and acronyms. The complete medicine names have largely only been listed where it adds to an appreciation of the error, for example, where two medicines with similar names have been confused.

Examples of reporters' narratives describing individual incidents, included later in this review, have been minimally edited for clarity, regarding grammar, abbreviations and jargon, with the intention of allowing a better understanding of exactly what took place. Wherever possible, they have been reproduced as they were received by the NRLS.

Across all the categories of incident reports, a number of common themes emerged in the qualitative analysis. Exemplar incidents with clinical outcomes of both actual and potential harm have been used to assist learning. When an error occurs it is often the culmination of more than one specific event, particularly for those events which result in serious patient harm. Accordingly, many of the incidents chosen to illustrate a particular theme could equally be used within other themes. For example, serious patient harm as a result of a failure to prescribe a medicine correctly according to a clinical trial protocol could be utilised to illustrate several of the themes set out below.

Table 4. Anti-cancer medicines incidents by medicine or therapeutic group

Anti-Cancer Medicine	All reports	Wrong, unclear dose, frequency, quantity	Omitted medicine	Wrong medicine	ADR and Allergy	Wrong Expiry	Wrong Label	Wrong Storage	Wrong method of preparation and mismatched patient	Other and Unknown
Taxanes	436	83 (19%)	56 (13%)	39 (9%)	120(28%)	27 (6%)	7 (1.5%)	7 (1.5%)	6 (1.4%)	59 (14%)
Cisplatin	404	121 (30%)	79 (20%)	32 (8%)	17 (4%)	23 (6%)	8 (2%)	32 (8%)	11 (3%)	61 (15%)
Etoposide	396	88 (22%)	76 (19%)	11 (3%)	69(17%)	40(10%)	14(4%)	44(11%)	7 (2%)	69(17.5%)
Capecitabine	368	203 (55%)	35 (9.5%)	26 (7%)	5 (1.5%)	6 (1.5%)	18 (5%)	1 (0.3%)	14 (4%)	46(12.5%)
Cyclophosphamide	359	140 (39%)	67 (19%)	28 (8%)	4 (1%)	7 (2%)	19 (5%)	9 (2.5%)	14 (4%)	51 (14%)
Carboplatin	325	87 (27%)	37 (11%)	25 (8%)	71(22%)	19 (6%)	3 (1%)	5 (1.5%)	7 (2%)	67 (20%)
Cytarabine	267	70 (26%)	87 (33%)	9 (3%)	3 (1%)	11 (4%)	10 (4%)	14 (5%)	13 (5%)	47 (18%)
Vinca Alkaloids	247	84 (34%)	32 (13%)	18 (7%)	11(4.5%)	10 (4%)	18 (7%)	5 (2%)	10 (4%)	44 (18%)
Methotrexate	231	77 (32%)	55 (24%)	8 (3.5%)	6 (2.5%)	5 (2%)	10 (4%)	6 (2.5%)	11 (5%)	46 (20%)
Oxaliplatin	202	72 (36%)	17 (8.5%)	23(11%)	39(19%)	9 (4.5%)	2 (1%)	0	6 (3%)	25 (12%)
Trastuzumab	168	56 (33.3%)	28 (17%)	11(6.5%)	4 (2%)	5 (3%)	2 (1%)	1 (0.5%)	11 (6.5%)	43 (26%)
Mitomycin	165	31 (19%)	31 (19%)	21(13%)	3 (2%)	4(2.5%)	5 (3%)	4 (2.5%)	17 (10%)	45 (27%)
Gemcitabine	135	46 (34%)	16 (12%)	16(12%)	4(3%)	7 (5%)	2(1.5%)	6 (4.5%)	3 (2%)	32 (24%)
Doxorubicin	127	44 (35%)	20 (16%)	6 (5%)	9 (7%)	8 (6%)	12(9.5%)	5 (4%)	3 (2%)	18 (14%)
Epirubicin	117	34 (29%)	15 (13%)	12(10%)	12(10%)	1 (1%)	6 (5%)	3 (2.5%)	2 (2%)	29 (25%)
Ifosphamide	94	19 (20%)	30 (32%)	2 (2%)	3 (3%)	9 (9%)	4 (4%)	3 (3%)	4 (4%)	18 (19%)
5FU	86	19 (22%)	25 (29%)	11(13%)	5 (6%)	3 (3.5%)	1 (1%)	2 (2%)	4 (4.5%)	14 (16%)
Mesna	80	28 (35%)	22(27.5%)	2 (2.5%)	2 (2.5%)	6 (7.5%)	2 (2.5%)	2 (2.5)	2 (2.5%)	10(12.5%)
Hydroxycarbamide	76	31 (41%)	8 (10.5%)	14(18%)	0	0	5 (6.5%)	0	6 (8%)	8 (10.5%)
Fludarabine	72	33 (46%)	11 (15%)	4 (5.5%)	0	3 (4%)	3 (4%)	2 (3%)	2 (3%)	11 (15%)
Irinotecan	53	13 (23%)	6 (11%)	14(26%)	3 (5.5%)	2 (3.5%)	2 (3.5%)	0	2 (3.5%)	9 (17%)
Bleomycin	51	12 (24%)	13 (25%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	3 (6%)	2 (4%)	12 (24%)
Melphalan	52	14 (27%)	13 (25%)	7(14%)	0	3 (6%)	2 (4%)	3 (6%)	0	10 (20%)
Busulphan	46	15 (33%)	10 (22%)	4 (9%)	0	5 (11%)	0	2 (4%)	3 (6.5%)	5 (11%)
Chlorambucil	44	13 (23%)	7 (16%)	8 (18%)	0	0	3 (7%)	3 (7%)	3 (7%)	7 (16%)
Cetuximab	43	14 (33%)	6 (14%)	4 (9%)	2 (4.5%)	5(12%)	2 (4.5%)	1 (2.3%)	2 (4.5%)	7 (16%)
Daunorubicin	36	9 (25%)	6 (16.6%)	3(8.3%)	0	3 (8.3%)	4 (11%)	4 (11%)	1 (3%)	6 (16.6%)
Temozolomide	25	14 (56%)	1(4%)	2 (8%)	0	0	3 (12%)	0	1 (4%)	4 (16%)
Bortezomib	22	4 (18%)	7 (32%)	0	0	2 (9%)	2 (9%)	0	2 (9%)	5 (23%)
Idarubicin	21	5 (24%)	2 (10%)	1 (5%)	0	6(29%)	2 (10%)	1 (5%)	0	3 (14%)
Mitoxantrone	21	7 (33%)	2 (9.5%)	1 (5%)	2 (9.5%)	3 (15%)	1 (5%)	1 (5%)	1 (5%)	0
Rituximab	16	2 (12.5%)	4 (25%)	3 (19%)	1 (6%)	1 (6%)	1 (6%)	0	1 (6%)	3 (19%)
Imatinib	19	5 (26%)	1(5%)	1(5%)	1(5%)	0	0	0	0	8 (42%)

3. Qualitative analysis

3.1 Method

A senior pharmacist with extensive experience in cancer therapy reviewed and undertook qualitative analysis of all patient safety incidents with reported clinical outcomes of death, severe and moderate harm and randomly sampled no harm reports. Themes were identified and example incidents extracted. A second senior pharmacist and a senior nurse provided a second review of the initial qualitative analysis. This second analysis was then subjected to a third review by a multidisciplinary group consisting of senior specialist doctors, nurses and pharmacists and following this review the final analysis was prepared.

Eight main themes were identified from the qualitative analysis of the data and a summary is presented here. More detail and examples of these themes can be found in Appendix 1 of the support materials to this themed review available at:

<http://www.nrls.npsa.nhs.uk/resources/?entryid45=75475>

4. Recommendations

Following qualitative analysis of these patient safety incident reports, a series of recommendations were developed as suggestions of good practice for local implementation and monitoring in order to improve care and minimise risk in relation to anti-cancer medicines.

Recommendations and examples of tools and safe practice were developed for the main themes.

4.1 Clinical protocols, prescriptions and documentation

Clinical protocols, prescriptions and all other documentation regarding anti-cancer medicines should be written in a clear and unambiguous manner to minimise misunderstanding and error. All anti-cancer treatment protocols should be risk assessed by the organisation producing them and human factors and practical implementation factors that can lead to errors in practice should be considered. Changes should be made to protocols to minimise risks of misinterpretation and reduce the likelihood of failure to follow them in practice.

- a) Minimise the use of abbreviations of any kind, even if they are considered to be well understood and in common use.
- b) The sole use of acronyms to identify the intended anti-cancer protocol should be minimised. Where it is essential that acronyms are used, either on paper or electronic systems, they should always be supported by the full names and doses of the constituent medicines and the intended tumour site. Decisions regarding the creation of acronyms for anti-cancer medicine protocols should be made in the context of those already in widespread use, for example, OPCS 4.5 Chemotherapy Medicine Protocols.¹
- c) Where the different treatment arms of a clinical trial are associated with different anti-cancer medicine protocols, the naming of the arms should be clear and unambiguous and make explicit reference to the medicines and doses they contain.
- d) When standard anti-cancer medicine protocols are modified in response to individual patient circumstances the alterations must be explicit and recorded in the patient's notes, treatment record and anti-cancer medicine prescription.
- e) Anti-cancer medicines should be prescribed by generic name and if appropriate, the specific formulation and its proprietary name. The dose, frequency and duration of treatment should always be written out in full.

- f) All prescriptions for anti-cancer medicines should specify the start and stop dates, the duration of treatment, and the number of days 'off treatment'.
- g) Comprehensive directions for use are especially important for oral anti-cancer medicine medicines. They must never be supplied and labelled 'To be taken as directed' unless the patient is receiving additional explicit verbal and written information regarding dose and frequency of administration, for example, paediatric oncology patients.

Example incidents that help to illustrate recommendation 1

A patient was on the third cycle of rescue anti-cancer medicines for relapsed Non-Hodgkins Lymphoma (NHL) in the form of PECC anti-cancer medicine (Prednisolone, Etoposide, Chlorambucil, CCNU [Lomustine]). He had received two prior cycles of prednisolone 40 mg per day for 7 days, etoposide 400 mg per day for 3 days, chlorambucil 40 mg od for 4 days and CCNU (lomustine) 200 mg per day for 1 day. The prescription for the third cycle was written as; Prednisolone 40 mg od x 7 / 7 Etoposide 400 mg od x 3/7 Chlorambucil 40 mg od x 4 / 7 and CCNU 200 mg od x 1 / 7

The outpatient pharmacy misread the 3 as an 8 for the etoposide and misinterpreted the 1 / 7 for the CCNU as 1 week instead of 1 day. Despite checking with an oncology pharmacist the incorrect amounts were dispensed. The patient was a prisoner in HMP and the medicines were returned to the prison with him.

The hospital prescription was transcribed to a prison prescription and the patient received the full amount of the medicines as (in)correctly prescribed. This was despite the patient raising concerns with the prison medical services that he was receiving more medicines than before in previous cycles. He was subsequently admitted to the acute hospital trust, 10 days after commencing his third cycle.

Following his emergency admission subsequent investigations revealed the prescribing error... (DEATH)

A patient had been changed from OxMdG (Oxaliplatin/Modified de Gramont), which contains 5-fluoruracil to Oxaliplatin and Capecitabine. The protocol selected from the computer by the clinic nurse was Oxycap and the patient received the first cycle. Upon returning for the second cycle it was discovered that the patient should have received XelOx. On the computer, the protocol name Oxycap actually referred to an arm of the FOCUS 2 Trial which delivered a 30% dose reduction of the two medicines (NO HARM).

An example of a protocol risk assessment checklist is available as part of the support materials for this themed review on the NPSA website.

4.2 Policies and procedures

Healthcare organisations should establish clear policies and procedures concerning which members of staff are authorised to prescribe and perform other duties with anti-cancer medicines, and it should cover all oncology professionals, including doctors, nurses and pharmacists. These policies and procedures should specify the training, competencies and methods of assessment of those staff considered appropriate to prescribe anti-cancer medicine. They should also provide guidance for non-cancer staff when dealing with anti-cancer medicine. Any staff not authorised by the trust should be prevented from prescribing anti-cancer medicine and this stance is echoed in the recommendations of the NCEPOD SACT Report².

Example incident that helps to illustrate recommendation 2

An F2 doctor was prescribing anti-cancer medicines (with an electronic prescribing system) whilst the consultant, the system administrator and the oncology pharmacist were all on annual leave. The serum creatinine level was not automatically entered into the system so the doctor tried to manually enter the result into the computer resulting in an incorrect level being entered and a low (calculated) CrCl being calculated. This resulted in a very low dose of carboplatin, which the doctor then amended manually by changing the AUC to 30.1, resulting in a 500% dose increase. (NO HARM)

The same patient returned to the anti-cancer medicine clinic three weeks later and was seen by a second F2 doctor who also had little or no electronic prescribing training and was also left to prescribe anti-cancer medicines without the consultant present (he planned to check the prescriptions the following day) but with the help of the system administrator. The system administrator noticed that the system had remembered the previous (high) AUC and it had recalculated the new dose of carboplatin to 4875mg. The AUC was changed to the correct level and dose was reduced. (NO HARM)

An example of a policy defining prescribing responsibilities for anti-cancer medicines is available as part of the support materials for this themed review on the NPSA website.

4.3 Modified protocols

Where anti-cancer medicine protocols are modified, or deviate from the standard version routinely used within an organisation, a new prescription should be generated. If this is not possible, any amendments must be clear and unambiguous. Furthermore, when standard anti-cancer protocols are modified in response to individual patient circumstances, the changes should be explicitly and unambiguously stated in all documentation. The term 'modified' is not sufficiently descriptive to be used safely.

Example incident that helps to illustrate recommendation 3

A patient was prescribed the CHLVPP anti-cancer regimen, but notes previously written by consultant stated that patient should have "*modified* CHLVPP". The nurse specialist understood this to mean that the patient was not to receive the vinblastine element of the anti-cancer medicine which had been prescribed. Had they not intervened, vinblastine would have been prepared and administered. (NO HARM)

4.4 Supporting treatments

When patients are receiving complicated (in-patient) protocols including supporting treatment, for example, mesna or hydration fluids, there needs to be adequate safeguards in place for prescribing, dispensing and administering these medicines alongside the anti-cancer medicines. Wherever possible, there should only be one anti-cancer medicine prescription containing details of all the medicines the patient requires for each cycle. This should include supportive treatments such as anti-emetics and antibiotics. Sequential infusions should be labelled to minimise the risk of them being missed.

Example incident that helps to illustrate recommendation 4

It was discovered that a patient did not receive all her required mesna hydration fluids to prevent haemorrhagic cystitis caused by her ifosfamide dose. She received a 900mg bolus of mesna prior to the ifosfamide plus a 1L bag of dextrose/saline plus mesna over 8hrs following the ifosfamide. When this bag was finished, the nurse looked at the next fluid bag which was dated the following day. The dates on the bags had been changed due to delays in commencing the anti-cancer medicine. However, the second bag of hydration should have retained its original date. The nurse thought the fluids would re-commence when the patient received their 2nd dose of Ifosfamide. Due to this error the patient experienced painful cystitis and could not receive her second and third doses of doxorubicin and ifosfamide. (SEVERE HARM)

An example of a combined anti-cancer medicine and supportive care prescription is available as part of the support materials for this themed review available on the NPSA website.

4.5 Electronic prescribing systems

Organisations should have robust clinical governance systems for setting up anti-cancer medicines onto electronic prescribing systems. These systems should include assigned responsibilities, and systems for double checking and validation. They should include the use of test prescriptions to validate that the correct doses are generated for the full range of treatment conditions and patient circumstances.

Example incident that helps to illustrate recommendation 5

A clinical trial patient was admitted to hospital as he was acutely breathless. Scans from three days earlier demonstrated pulmonary fibrosis, pulmonary embolisms and a small pneumothorax. After three days on the oncology ward the patient was then transferred to ITU, where he died a further three days later of pulmonary fibrosis related to bleomycin. Following his death, it was discovered by the trial nurse that the patient had received too high a dose of bleomycin on seven separate occasions. This was as a result of the trial anti-cancer medicines protocol being incorrectly set up on the Trust electronic prescribing system. (DEATH)

A standard operating procedure for the creation of anti-cancer medicine protocols on an electronic prescribing system is available as part of the support materials for this themed review on the NPSA website.

4.6 Additional precautions with oral anti-cancer medicines

In 2008, the NPSA published the Rapid Response Report (RRR) NPSA/2008/RRR001 *Risks of incorrect dosing of oral anti-cancer medicines*³. This RRR recommends that additional precautions are required for oral anti-cancer medicines to ensure that these medicines are used safely. The protocol or patient held treatment plan should be checked every time these medicines are prescribed, dispensed and first administered.

Patients should be better informed and more actively involved in their anti-cancer medicine treatment. The use of patient held treatment plans for oral anti-cancer medicines can usefully summarise the use of anti-cancer medicines for an individual patient. They may contain information on doses, frequency and duration of treatment cycles, dates and times of monitoring, details of key contacts, early signs of possible toxicity and what action to take. (See also the National Chemotherapy Advisory Group Report (NCAG) 2009⁴).

When oral anti-cancer medicines are dispensed, the quantity of tablets/capsules should always be double-checked as part of the final check of the prescription and again by the person who issues them to the patient. Pharmaceutical manufacturers should be encouraged by the NHS to develop clearly distinguishable packs, containing quantities of tablets which more accurately reflect the way their medicines are prescribed and dispensed^{5,6}. This may reduce the number of manipulations required during the dispensing process and reduce the risk of errors.

Example incidents that help to illustrate recommendation 6

A GP saw and assessed a patient with a chest infection and was aware that the patient had started anti-cancer medicine for carcinoma of the oesophagus the previous week. However, the GP was not aware that this anti-cancer medicine could cause anaemia and that if the patient developed an infection a full blood count should be performed. The patient declined admission and he was managed at home for three days until his condition became markedly worse. He was admitted to hospital and died six days later of cardio-respiratory failure secondary to septic shock. The GP had not initially considered admission as both the patient and his wife were keen for him to remain at home.

Whilst talking over the event with his widow, she asked the GP if the anti-cancer medicines could have contributed to his death. When the GP checked, it was discovered that on admission the patient had a pancytopenia (a reaction to one of the three chemotherapeutic agents) and a creatinine > 300 (a reaction to another of the agents). Anti-cancer medicine was not mentioned as a contributing factor in his death. Further investigation by the GP revealed that the routine letter from the oncologist had been received by the surgery, arriving on Christmas Eve just prior to its early closure. The letter warned of the possibility of neutropenic sepsis, however the surgery had a backlog of over 400 unopened letters and the letter was only read by a second GP after the patient's admission to hospital. (DEATH)

Patient attended for first cycle of ECX anti-cancer medicine. The capecitabine (Xeloda) tablets were counted out with patient and it was found they had been supplied with 210 tablets instead of 105 as prescribed. Pharmacy informed and item re-dispensed. (NO HARM)

An example patient held treatment plan for oral anti-cancer medicines is available as part of the support materials for this themed review available on the NPSA website.

4.7 Monitoring of infusional therapy

Patients receiving infusional anti-cancer medicine regulated by a device of any kind should undergo regular monitoring (as defined by the organisation), using a monitoring form to ensure that the rate and amount of delivered medicine is as expected.

Example incident that helps to illustrate recommendation 7

A patient was prescribed a dose of IV fluorouracil of 2,575mg to be infused over seven days at home via a portable elastomeric infusion device. The dose should have been administered in a 1.5ml / hr infusor, but was dispensed in a 5ml / hr infusor in error. The patient received the total dose over three days rather than seven and returned to clinic concerned that the infusion had finished ahead of schedule. (LOW HARM)

An example infusional anti-cancer medicine monitoring form is available as part of the support materials for this themed review on the NPSA website.

4.8 Managing toxicities of anti-cancer medicines

It is important that toxicities to anti-cancer medicines are recognised and treated promptly, particularly if the patient presents to a non-oncology setting. Outcomes may be improved by:

- ensuring patients and carers are well-informed regarding the treatment and possible side effects and where necessary contact specialist staff with training and experience in managing oncology toxicity on the 24 hour number provided to the patient;
- ensuring that when cancer patients are seen or admitted by non specialist staff, procedures are in place whereby patients are quickly identified as being or having been on anti-cancer medicines. This is then clearly noted in the clinical record and guidance on management sought from specialist staff with training and experience in managing oncology toxicity;
- reinforcing that the 24-hour number contact number, issued to patients, can also be used by healthcare staff to obtain advice from cancer specialist staff.

Example incident that helps to illustrate recommendation 8

A patient with bowel cancer was receiving oral capecitabine and IV oxaliplatin. Five days after commencing the capecitabine he developed rapid onset of chest pain and was admitted on the same day with a confirmed myocardial infarction. He subsequently underwent primary PTCA (Percutaneous Transluminal Coronary Angioplasty) catheterisation for mild LV dysfunction and double vessel disease. Cardiotoxicity is a rare complication of oral capecitabine, however the patient was allowed to continue on it whilst he was an inpatient. Additionally, he was prescribed a further five days supply of capecitabine, over and above his current prescribed dose on discharge from hospital by a non-oncology doctor. Fortunately, the patient didn't take the additional tablets. (MODERATE HARM)

A toxicity recognition guide is available as part of the support materials for this themed review on the NPSA website.

4. 9 Tests and investigations relevant to the safe prescribing of anti-cancer medicines

Tests and investigations relevant to the safe prescribing of anti-cancer medicines should be carried out, verified and documented prior to prescription and administration. In the event of abnormal test results, appropriate action or advice should be taken and any supportive medication should be commenced.

Example incident that helps to illustrate recommendation 9

A patient had been appropriately reviewed as per protocol, including having a new full blood count, as they were due to receive vinorelbine 50mg. The neutrophil count was documented as 1.2 by the clinic nurse and vinorelbine was given according to protocol. The patient was re-admitted the same day with rigors and temperature with a neutrophil count of 0.9. At this level the vinorelbine should not have been given and treatment should have been delayed. The patient remained an inpatient for six days as a result. Blood results are not usually double checked in clinic and the reported pre-treatment result of 1.2 did not correspond with anything else on the haematology results for the patient. It was unclear who/how the error was made. (MODERATE HARM)

Information in this report reiterates the importance of basing treatment decisions on timely, verifiable laboratory values. In the case of this patient, it was unclear when the original neutrophil count of 1.2 had been obtained, particularly as no reference could be found to it in the patient's laboratory records. Patient safety is severely compromised by making decisions on uncertain data.

5. Conclusion and discussion

Analysis of these patient safety incident reports has provided a unique insight into the challenges faced by staff and patients in delivering safe, effective and timely anti-cancer medicine. The potential toxicities of anti-cancer treatments are well known and organisations have developed systems to minimise the risk to patients, however patient safety incidents do still occur. A total of 4,829 patient safety incident reports regarding anti-cancer medicines were received between November 2003 and June 2008. This was out of a total of nearly 219,000 patient safety incident reports relating to medication received by the NRLS over the same period. Nine patient deaths (0.17 per cent) were reported, which on review were validated as seven reports of death including one report of severe harm and one of moderate harm where the patients had actually died according to the text of the report.

Within an organisation, an incident resulting in the death of a patient or severe lasting harm will provoke an investigation into the causes and the appropriate remedial action will be undertaken. While the circumstances leading up to the error may be considered unique to the individual organisation, this may not be the case. If the incident and learning is shared with the wider professional community through the NRLS, then it can reduce the likelihood of a similar event occurring elsewhere.

Conversely, the detail of incidents where there has been insignificant or no adverse patient outcome may be largely ignored. In the many reports where the patient harm was identified as minimal, a satisfactory outcome has been largely attributable to the diligence of professional staff. Anecdotally, it has been observed that there is often very little sharing and learning from these 'minor' events within an organisation. Wider sharing across healthcare organisations and cancer networks is unusual.. It is suggested that, in conjunction with cancer care commissioners, all cancer networks establish a mechanism for sharing error reports to all their providers.

Within both major and minor incidents it has been possible to observe a number of consistent themes emerge, which have been highlighted in the report. From these themes it has been possible to propose a number of individual recommendations to improve patient safety. It is acknowledged that many organisations may already have appropriate processes in place as part of their own ongoing quality and governance initiatives.

Further consideration of the themes and subsequent recommendations has suggested poor information quality may be at the heart of many episodes of patient harm. Anti-cancer medicine is a complex therapeutic area and there is an overwhelming amount of information available regarding all aspects of it. In an attempt to elicit and maintain a manageable personal library of knowledge that is relevant to patient care, most professionals will routinely use a limited number of key sources. One of these key sources is the 'anti-cancer medicine protocol'.

There is not one definition of an anti-cancer medicine protocol. In the context of malignant disease it may be broadly described as *a body of facts containing all the necessary information to facilitate the safe, effective and appropriate delivery of one or more anti-cancer medicines in a defined schedule to a patient with a specific cancer*. However, while anti-cancer medicine protocols commonly contain the same types of information, there is no clear guidance as to how the protocol should be constructed and presented.

Anti-cancer medicine protocols in common use often have their origins in the trials that demonstrated their benefit. A lasting legacy of this link may be the acronym generated to identify the anti-cancer medicine protocol. There is a huge lexicon of anti-cancer medicine protocol names and acronyms, but no consistency in how they are created and the same

acronym may refer to more than one combination of medicines. Many reported errors involved confusion with acronyms, not least because they do not provide details of the medicines and doses of the medicines they actually refer to.

Changes in the way that healthcare organisations are funded for procuring and delivering anti-cancer medicine may also influence the choice of future protocol names. National anti-cancer medicine protocol lists have been compiled, but these currently merely reflect the names in existing use throughout the country and further afield. It has proved challenging to organise and update the list in a systematic manner. There is an increasing awareness that in the future there will be a significant link between a protocol name/acronym and the remuneration to be associated with it. Clinical and financial governance imperatives may drive a greater degree of clarity and standardisation of protocol names.

The National Cancer Research Institute (NCRI) which co-ordinates many of the large cancer trials undertaken across the country has a Chemotherapy and Pharmacy Advisory Service (CPAS) which advises on practical aspects of forthcoming NCRI sponsored trials. It is possible that the remit of this group could be widened to include risk assessment of individual clinical trial protocols and the development of a generic checklist to risk assess protocols. Such a checklist would clearly have a very wide applicability among providers of anti-cancer medicine services and such schemes have been shown to reduce patient harm in other clinical areas such as surgery⁷. However, it is unclear whether the significant number of non-NCRI and commercial clinical trials are currently reviewed in a similar manner.

Current European legislation governing clinical trials is comprehensive, with the aim of protecting patients. But despite this, clinical trial design can sometimes contribute to serious and even fatal errors. Combined with the information required to fully answer the therapeutic questions being addressed, complying with the legislation can result in complex trial protocol documentation, often running into several hundreds of pages. Reported errors involved misinterpretations of the information about trials themselves and as a result of mistakes introduced when information was re-drafted for local use, commonly for an electronic prescribing system.

Electronic prescribing software is being increasingly used to support the prescribing and delivery of anti-cancer medicines and systems may be supplied with a library of 'standard' anti-cancer medicine protocols. It cannot be assumed that they do not contain any major errors and will therefore still require rigorous validation in line with local governance guidelines. Protocols that are used within clinical trials can often be unique and will require creation from scratch by an organisation. Failure to adequately validate a new or non-standard protocol may allow a mistake during the creation of an electronic version to remain undetected until it yields an error resulting in patient harm. Furthermore, following an error involving electronic prescribing systems it is important to ensure that any erroneous data inputted by users, as opposed to those maintaining the system, is removed to prevent it from contributing to further errors. This has resource implications for NHS organisations as the appropriately qualified professionals required for the implementation and governance of electronic prescribing systems are not always available.

General medicine information sources (e.g. the *British National Formulary*) contain summary information about anti-cancer medicines. These sources mostly provide information about the licensed use of individual anti-cancer medicines and do not adequately convey the complexities of multi-medicine protocols, complex dosing, off label use of these medicines in clinical trials, or sufficient details concerning monitoring and management of toxicities.

Anti-cancer medicine information, in addition to the general medicine information sources, is required by specialists and non-specialists to ensure the safe use of the anti-cancer medicine.

RRR001 *Risks of incorrect dosing of oral anti-cancer medicines*³ (See Section 4.6: Additional precautions with oral anti-cancer medicines, above) recommends that non-specialists who prescribe, dispense or administer these medicines should have ready access to appropriate treatment protocols and treatment plans.

Patients should also be fully informed and receive verbal and up-to-date written information about their oral anti-cancer therapy from the initiating hospital. This information should include contact details for specialist advice, which can be shared with non-specialist practitioners. Written information, including details of the intended oral anti-cancer protocol, treatment plan and arrangements for monitoring, taken from the original protocol should be given to the patient. When shared with pharmacists and dispensing staff, this would enable the above dispensing requirements to be satisfied. The British Oncology Pharmacy Association (BOPA) has also developed standards for the validation of prescriptions for cancer medicines⁸ and a supporting guidance document⁹.

Where appropriate, use should also be made of NHS trust and cancer network websites to provide information for healthcare staff, patients and carers to assist in the safe use of oral anti-cancer medicines.

In summary, it would appear that poor protocol presentation and documentation, and poorly planned and managed implementation have a significant influence on a wide range of apparently unconnected anti-cancer medicine incidents. Protocols are often created to meet a very individual set of needs. These include those of pharmaceutical companies, clinical trial investigators, clinicians and provider organisations, often without reference to other similar documents that may already exist or with a true impression of how they will be applied in practice.

Standardisation of protocols, particularly in respect of their nomenclature including abbreviations and acronyms, content and layout and consideration of how they may be interpreted in a working environment would represent a major advance in terms of the safety of anti-cancer medicine. It is possible this may be achieved by using a checklist approach when designing and producing protocols to ensure that specific areas have been addressed.

6. References

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- 7) World Health Organization. *Surgical Safety Checklist.* WHO, 2008. Available at: www.who.int/patientsafety/safesurgery/ss_checklist/en/index.html
- 8) British Oncology Pharmacy Association (BOPA) *BOPA Standards for Clinical Pharmacy Verification of Prescriptions for Cancer Medicines* Jan 2010 (Final). Available at www.bopawebsite.org/tiki-page.php?pageName=Position+Statements
- 9) British Oncology Pharmacy Association (BOPA) *Guidance to Support BOPA Standards for Clinical Pharmacy Verification of Prescriptions for Cancer Medicines v1.5* Feb 2010 Available at www.bopawebsite.org/tiki-page.php?pageName=Position+Statements

7. Search terms

All incidents reported to the NRLS between 1 November 2003 and 30 June 2008 were reviewed. The following search terms were used to search the NRLS database to identify incident reports relating to anti-cancer medicine

Alimta	Fludara	Porfimer
Alkeran	Fludarabine Phosphate	Procarbazine
Amsacrine	Fluorouracil	Protein Kinase Inhibitors
Amsidine	Foscan	Puri-Nethol
Arsenic Trioxide	Gemcitabine	Raltitrexed
Atriance	Gemzar	Sorafenib
Avastin	Gliadel	Sprycel
Bevacizumab	Glivec	Sunitinib
Bexarotene	Herceptin	Sutent
Bicnu	Hycamtin	Tarceva
Bleomycin	Hydrea	Targretin
Bortezomib	Hydroxycarbamide	Taxanes
Busilvex	Hydroxyurea	Taxol
Busulfan	Idarubicin	Taxotere
Busulphan	Ifosfamide	Tegafur
Caelyx	Imatinib	Temodal
Campto	Irinotecan	Temoporfin
Capecitabine	Lanvis	Temozolomide
Carboplatin	Leukeran	Thioguanine
Carmustine	Leustat	Tioguanine
Cetuximab	Litak	Thiotepa
Chlorambucil	Lomustine	Tomudex
Cisplatin	Lysodren	Topoisomerase I Inhibitors
Cladribine	Melphalan	Topotecan
Clofarabine	Mercaptopurine	Trabectedin
Cosmegen Lyovac	Methotrexate	Trastuzumab
Crisantaspase	Mitobronitol	Treosulfan
Cyclophosphamide	Mitomycin	Tretinoin
Cytarabine	Mitotane	Trisenox
Dacarbazine	Mitoxana	Uftoral
Dactinomycin	Mitoxantrone	Uracil
Dasatinib	Mitozantrone	Velbe
Daunorubicin	Myleran	Velcade
Daunoxome	Myocet	Vepesid
Depocyte	Navelbine	Vesanoid
Docetaxel	Nelarabine	Vinblastine
Doxorubicin	Nexavar	Vincristine
Eloxatin	Nipent	Vindesine
Endoxana	Oncovin	Vinorelbine
Epirubicin	Onkotrone	Xeloda
Erbitux	Oxaliplatin	Yondelis
Erlotinib	Paclitaxel	Zevali
Erwinase	Paraplatin	
Estracyt	Pemetrexed	
Estramustine	Pentostatin	
Etopophos	Pharmorubicin	
Etoposide	Photofrin	
Evoltra	Platinum Compounds	