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SHORT COMMUNICATION

Incidence of Contrast-Induced Nephropathy in Patients with Multiple Myeloma Undergoing Contrast-Enhanced Procedures

Maeve P. Crowley[1] · **Vinitha N. Prabhakaran**[2] · **Oonagh M. Gilligan**[1]

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Abstract Multiple myeloma (MM) is a malignant disorder characterized by clonal proliferation of plasma cells. Renal impairment is a common complication. Contrast-induced nephropathy (CIN) is a form of acute renal failure that can occur in the setting of IV contrast administration. It is more commonly seen in patients with pre-existing renal impairment. Patients with MM commonly require contrast enhanced procedures. The literature regarding the safety of IV contrast in this cohort is lacking. A retrospective review was carried out in a university hospital to identify the incidence of CIN in patients with MM and to look for associated risk factors. 94 patients and 165 procedures were included in the analysis. 10% of procedures resulted in CIN. 59% (10/17) of creatinines had normalized within one month of the procedure. The only factor found to be significant for the development of CIN was the timing of the procedure (<18mths verses >18mths post diagnosis of MM; $p = 0.045$). CIN appears to occur at an increased rate in patients with MM. However this may be an over-estimation given the common occurrence of renal impairment in this cohort and the close temporal relationship which often exists between systemic illness and contrast-enhanced procedures.

✉ Maeve P. Crowley
maeve.crowley@gmail.com

Vinitha N. Prabhakaran
109122656@umail.ucc.ie

Oonagh M. Gilligan
Oonagh.Gilligan@hse.ie

[1] Department of Haematology, Cork University Hospital, Wilton, Cork, Ireland

[2] Department of Medicine, University College Cork, Cork, Ireland

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Background

Multiple myeloma (MM) is a malignant disorder characterised by uncontrolled clonal proliferation of plasma cells derived from B lymphocytes in the bone marrow [1]. In the United States, the lifetime risk of getting MM is 1 in 149 with an estimated 22,350 new cases being diagnosed in 2013 alone [2]. The incidence in Ireland is 5.3 cases per 100,000 per year and the median age at diagnosis is 71 years. Men are affected more commonly than women [3]. It has been shown that almost one quarter of patients with MM have renal failure at diagnosis and the severity of the renal failure is significantly associated with survival [4]. Multiple pathogenic mechanisms can contribute to kidney injury in MM, some of which are the result of nephrotoxic monoclonal immunoglobulins and some of which are independent of paraprotein deposition [5]. Dehydration, aminoglycoside antibiotics and the administration of intravenous (IV) contrast during radiological procedures can all exacerbate renal impairment in the setting of MM, with the later possibly leading to contrast-induced nephropathy.

Contrast-induced nephropathy (CIN) is a reversible form of acute renal failure. It can be defined as a > 25% increase or a rise of more than 0.5 mg/dL in serum creatinine level above baseline after receiving IV or intra-arterial contrast material [6]. It occurs within three days of administration of contrast media in the absence of an alternative aetiology [7]. The pathophysiology is complex and only partially understood. It appears to have three branches that interact with each other: haemodynamic effects, formation of reactive oxygen species and tubular cell toxicity [8]. The occurrence of CIN depends

on multiple factors including physical and chemical characteristics and volume of the contrast agent, patient risk factors and preventative measures implemented prior to the procedure. Oncology patients are exposed to multiple nephrotoxic agents (cytotoxic drugs, antibiotics and analgesics). In addition, issues such as anaemia, hypercalcaemia and hyperuricacidemia may also lead to nephropathy leading to a higher quoted rate of CIN in these patients [9]. In a recent meta-analysis, the average rate of AKI in all studies was 6.4% [10].

The literature regarding the risk of CIN in patients with MM generally consists of small case series and small retrospective reviews. It is also often contradictory. Holman reported the first case of acute renal failure and death after IV contrast in a patient with MM in 1939 [11]. Fourteen other cases have also published supporting the link between CIN and MM [12–20]. In most of these cases, the patients had significant proteinuria and extensive cast formation in the renal tubules even before administration of the contrast. There is only one retrospective review of 39 patients [21] supporting the link. There are eight retrospective studies [22–29], one systematic review [30] and one randomized controlled trial [31] that reject the link. Most of the studies were small with only two studies having more than fifty patients. These were carried out in the 1960s and 1970s which means they may not be applicable to current practice. The aim of this study was to perform a retrospective review of all contrast-enhanced procedures performed on patients with MM from a large university hospital to investigate the incidence of contrast induced nephropathy in myeloma patients.

Methods

All patients with MM attending a university hospital between January 2007 and December 2012 were identified by searching the *Lantis* Oncology Information System (used to record out-patient activity) and the Hospital In-Patient Enquiry (HIPE) Scheme (used to record in-patient activity) for the terms *myeloma*, *multiple myeloma*, *smouldering myeloma, plasma cell leukemia, plasmacytoma, plasma cell disorder and monoclonal gammopathy of uncertain significance (MGUS)*. The medical records, including the pathology reports of the patients identified were reviewed to ensure that they met the inclusion criteria of having symptomatic multiple myeloma. The remaining patient records were then examined to ascertain patient demographics. To determine the number and type of contrast enhanced procedures that the patients with MM had undergone, The Radiology Information System (RIS) was consulted. The serum creatinine level within a 14-day period before contrast administration, the highest creatinine level within 3 days after the examination and the creatinine level at day thirty post contrast if a diagnosis of CIN was made were recorded. The uncorrected serum calcium in the 14-day period prior to contrast was recorded. A patients' international staging system (ISS) score was also recorded. Serum creatinine and calcium were measured by standard practice in our hospital's clinical laboratory. The study protocol was approved by the clinical research ethics committee of the institution.

CIN was defined as an increase as a > 25% increase or a rise of more than 44.2 mmol (0.5 mg/dL) in serum creatinine level above baseline after receiving IV contrast material within three days of administration of contrast media.

Data was described using mean and standard deviation (SD) or for nonparametric distributions using median and intra-quartile range (IQR). Comparison between groups was performed using Fisher's exact test for categorical variables and Mann-Whitney U-test or Kruskal-Wallis test for non-normally distributed continuous variables with two or more than two groups, respectively. Comparison between two non-normally distributed medians was performed using the Related-Samples Wilcoxan Signed Ranks Test. Analyses were performed using Predictive Analytical Software (PASW) Statistics, Version 18.0 using a two-sided type 1 error rate of 0.05.

Results

217 myeloma patients were identified. Fifty-two percent had received iodinated contrast (112 patients had undergone 240 procedures). Seventy-five procedures were excluded as patients were on dialysis or they did not have a serum creatinine performed in the two weeks prior to the procedure or in the three days after the procedure. This left 94 patients and 165 procedures for analysis. Table 1 summarises patient characteristics. The most common subtypes of myeloma were IgG, IgA and Light Chain. The mean (SD) number of procedures per patient was 2.1 (1.3). The baseline creatinine was elevated (upper limit of normal was 104 mmol/L) in 47 % (n = 77) and calcium was elevated in 1 % (n = 2). Table 2 shows the type and frequency of contrast enhanced procedures that were performed. Ten percent (17/165) of procedures resulted in Contrast-induced nephropathy (CIN). Fifty-nine percent (10/17) of creatinines had normalised within one month of the procedure. 17/94 patients developed CIN. No patient developed CIN on more than one occasion despite a mean (SD) contrast-enhanced procedure per patient of 2.1(1.3).

There was no statistically significant difference between the pre- and post-procedure creatinine (p = 0.079) Documentation regarding the volume of contrast administered, presence of infection, state of hydration and co-administration of nephrotoxic agents varied greatly so it was not factored into the analysis.

Table 1 Patient characteristics

Sex n (%)	
Male	59 (62.8)
Female	35 (37.2)
Mean (SD) age at diagnosis (years)	64.4 (11.8)
Median (IQR) duration of disease at time of procedure (months)	35 (22–56)
Myeloma Subtype n (%)	
IgG	44(46.8)
IgA	23 (24.5)
Light Chain	19 (20.2)
Non-secretory	4 (4.3)
IgD	3 (3.2)
IgM	1 (1.1)
International Staging System n (%)	
I	20 (20.3)
II	40 (42.6)
III	17 (18.1)
Unknown	17 (18.1)
Autologous Stem-cell Transplant n (%)	
Yes	23 (24.5)
No	71 (75.5)
Median (IQR) Albumin at diagnosis (g/L)	32.5 (28–37)
Median (IQR) β2-Microglobulin at diagnosis (mg/L)	3.16 (2.51–5.05)
Median (IQR) Creatinine (mmol/L) (Baseline)	87 (72.5–120)
Median (IQR) Creatinine (mmol/L) (Post Procedure)	90 (74–130)
Mean (SD) Calcium (mmol/L) (Baseline)	2.14 (0.23)
Mean (SD) number of contrast enhanced procedures per patient	2.1 (1.3)

Table 2 Univariate analysis

Patient characteristic	CIN Yes	CIN No	*p* value
Sex (n)			
Male	10	87	*1*
Female	7	61	
Age at Procedure (years) (n)			
0–49	1	15	*0.215*
50–59	6	29	
60–69	5	54	
70–79	5	28	
80–89	0	22	
Myeloma (n)			
IgG	6	68	*0.434*
IgA	5	31	
IgD	1	5	
IgM	1	2	
Light Chain	3	34	
Non-secretory	1	8	
International Staging System (n)			
I	1	33	*0.185*
II	6	61	
III	5	26	
Baseline Creatinine (n)			
Normal	10	78	*0.414*
Elevated	7	70	
Baseline Calcium (n)			
Normal	17	142	*0.515*
Elevated	0	6	
Type of Contrast Enhanced Procedure (n)			
CT	14	129	*0.402*
Non-CT	3	19	
Timing of Procedure (n)			
Within 18 Months of diagnosis	6	22	*0.045*
Beyond 18 Months of diagnosis	11	126	

$p < 0.05$ is significant to italic data

Univariate analysis was carried out to see if any patient characteristic was associated with an increased risk of developing CIN following a contrast-enhanced procedure (Table 2). The only factor that was significantly associated with development of CIN was the timing of the procedure ($p = 0.045$). This was confirmed on multivariate analysis where the odds of developing CIN was 3.124 higher if a patient had a contrast enhanced procedure in the first eighteen months after a diagnosis of myeloma was made rather than after that (95% CI 1.047–9.319, $p = 0.041$).

Discussion

MM is an increasingly prevalent malignancy with the relative five year survival increasing from 26.1% to 45.9% over the last ten years in Ireland [3]. Iodinated contrast medium is one of the most commonly prescribed agents in medicine. While contrast-enhanced procedures are not part of the standard evaluation of patients with MM, they are commonly performed given the increased incidence of infection and venous thromboembolism in this cohort. Renal impairment is one of the leading causes of morbidity and mortality in patients with MM. Given the known link between IV contrast and renal impairment, it is important to balance the risk of CIN and a patient's need for necessary contrast-enhanced diagnostic procedures.

Fifty-two percent of the available patients with MM had undergone at least one contrast-enhanced procedure and most had undergone more than one. The distribution of sex, MM subtypes and International Staging System (ISS) stage was similar to other published studies. Most patients (96%) had a

normal calcium level prior to the contrast-enhanced procedure. While both the median creatinine pre- and post-procedure were in the normal range, the median post-procedure creatinine was slightly higher. However, this difference was not significant ($p = 0.079$). CT (not angiogram) was the most frequently performed contrast enhanced procedure. Procedures relating to venous thrombosis accounted for one third (57/165) of those performed, underlining the prominent role of thrombosis in MM.

The overall rate of CIN in this cohort was 10 % which is higher than the rate quoted in a recent meta-analysis in a non-MM population (6.4%) [8] but lower than the incidence quoted in cancer patients (20%) [9].

The only statistically significant finding on univariate and multivariate analysis in this study was that the timing of the procedure in relation to the diagnosis of myeloma. Patients had a three-fold increased risk of developing CIN if they were scanned in the first eighteen months after diagnosis verses after that. This is suggestive of MM disease burden being an important risk factor for development of CIN in this cohort. While ISS stage was not significant, this may be due to the fact that the stage was unknown in 18 % of patients. This would correlate with a previously published study [28] that showed that β_2 –microglobulin levels, a marker of disease burden, correlated with the incidence of CIN.

The strengths of this study are that it is significantly larger than similar, recently published studies [28] and it takes into account all contrast-enhanced procedures that patients underwent rather than just CTs. Limitations include the retrospective nature of the study design, lack of information about volume of contrast administered and being a single centre study.

The risk of CIN should not be an absolute contraindication to contrast in the appropriate clinical setting, rather a reminder to minimize concomitant nephro-toxic agents and to give special attention to fluid balance at the time of the procedure. Contrast-enhanced imaging is often unavoidable in this population. Given the improved outcomes in MM with novel therapeutic strategies, it is important to monitor treatment related morbidity so that it doesn't negate the benefits of treatment. Both the American College of Radiologists and the Royal College of Radiologists in the United Kingdom have published general guidelines on CIN [32, 33]. While they do not specifically mention patients with MM, they lay out general measures that should be put into practice to minimise the occurrence of CIN.

Conclusion

CIN appears to occur at an increased rate in patients with MM. However this may be an over-estimation given the common occurrence of renal impairment in this cohort and the close temporal relationship which often exists between systemic illness and procedures.

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Vinitha N Prabhakaran performed the research and wrote the paper.
Oonagh M Gilligan designed the study and wrote the paper.

Compliance with Ethical Standards

Conflict of Interest Maeve P Crowley, Vinitha N Prabhakaran and Oonagh M Gilligan have no conflicts of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed Consent Following review at the institutional ethics board, it was deemed unnecessary to obtain informed consent from all individual participants included in the study as no identifying details would be included.

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