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Morris, K.A., Golding, J.F., Blesing, C., Evans, D.G., Ferner, R.E., Foweraker, K., Halliday, D., Jena, R., McBain, C., McCabe, M.G., Swampillai, A., Warner, N., Wilson, S., Parry, A. and Afridi, S.

This is an author's accepted manuscript of an article published in Journal of Neuro-oncology in 2016. doi:10.1007/s11060-016-2276-9

The final publication is available at Springer via:

https://dx.doi.org/10.1007/s11060-016-2276-9

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paper accepted 2016 for : Journal of Neuro-Oncology

Toxicity profile of bevacizumab in the UK Neurofibromatosis Type 2 cohort

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Running Title:

Bevacizumab toxicity in NF2 patients

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Key Words:

Neurofibromatosis type 2; cardiac failure; bevacizumab; hypertension; proteinuria; toxicity

Conflicts of interest:

No conflicts of interests for any of the authors.

Funding:

Dr Morris: NIHR RCF grant from the University of Oxford (AC12/092).

Body of text: 2888 words Abstract: 250 words

References 19 Figures: 2 Tables: 3

Abstract

Bevacizumab is considered an established part of the treatment strategies available for schwannomas in patients with Neurofibromatosis Type 2(NF2). In the UK, it is available through NHS National Specialized Commissioning to NF2 patients with a rapidly growing target schwannoma. Regrowth of the tumour on suspension of treatment is often observed resulting in prolonged periods of exposure to bevacizumab to control the disease. Hypertension and proteinuria are common events with bevacizumab use and there are concerns with regards to the long-term risks of prolonged treatment.

Dosing, demographic and adverse event(CTCAE 4.03) data from the UK NF2 bevacizumab cohort are reviewed with particular consideration of renal and cardiovascular complications.

Eighty patients (48 male:32female), median age 24.5 years (range 11-66years), were followed for a median of 32.7 months (range 12.0–60.2months). The most common adverse events were fatigue, hypertension and infection. A total of 19/80 patients (24%) had either a grade 2 or grade 3 hypertension event and 14/80 patients (17.5%) had proteinuria. Of 36 patients followed for 36 months, 78% were free from hypertension and 86% were free of proteinuria. Logistic regression modeling identified age and induction dosing regime to be predictors of development of hypertension with dose of 7.5mg/kg three weekly and age >30years having higher rates of hypertension. Proteinuria persisted in one of three patients after cessation of bevacizumab. One patient developed congestive heart failure and the details of this case are described.

Further work is needed to determine optimal dosing regimes to limit toxicity without impacting on efficacy.

Introduction:

Bevacizumab is now an established treatment option for Neurofibromatosis type 2 (NF2) associated schwannomas in the UK, Europe and the United States, with over 100 people being treated in the UK alone for rapidly growing schwannomas [1-8]. People with NF2 can suffer significant morbidity and mortality due to their disease and life expectancy is substantially reduced in more severe cases [9]. A reduction in size of cystic structures associated with a small group of ependymomas has also been reported [10,11](Morris et al 2016 submitted). Meningiomas while common in NF2 have been shown to respond to bevacizumab only briefly and only in a small minority of cases.[12,13]

Radiological response rates for schwannomas have been approximately 35-40% in all reported adult cohorts. The optimal timing and duration of treatment are yet to be identified. Longer breaks in treatment have been associated with tumour regrowth in some cases [3,6]. Therefore, once tumour growth has been controlled, UK practice has been to maintain tumour stability using a reduced dose intensity 'maintenance' regimen [6]. This approach has also been successfully used by another group when toxicities occur [1,7].

Hypertension and proteinuria are known adverse events associated with bevacizumab therapy in malignant disease [14] and in NF2 [3,15,4,6]. In addition, hypertension is more common in NF2 than in the general population. While age is a coexistent risk factor, even young patients with NF2 develop hypertension more frequently than age matched controls [16].

Bevacizumab is currently the only effective medical agent available for treating NF2-associated tumours. The impact on long-term health of hypertension and proteinuria and other bevacizumab-related toxicities are yet to be determined.

In this paper we present the adverse events in the UK NF2 bevacizumab cohort, the largest NF2 cohort to date, with particular attention to cardiac and renal adverse events.

Methods:

1) Study Cohort

The clinical records of 80 NF2 patients who commenced treatment with bevacizumab between August 2010 and November 2014 according to the UK national protocol were reviewed [6]. Bevacizumab treatment dose and the presence of any adverse events were recorded at each cycle of treatment alongside the need for any break in treatment. The following data were also collected: genetic severity [6], personal or family history of hypertension, concurrent medications, Body Mass Index (BMI) at baseline and smoking history. Mean arterial pressure (MAP) at infusion clinic and creatinine clearance (CrCl) calculated according to the Cockcroft-Gault equation were recorded over time. Data continued to be collected if the patient discontinued treatment.

2) Adverse events

All adverse events were recorded and classified according the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [17]. Hypertension according to NICE and AHA guidelines is defined as a blood pressure of ≥140/90 mmHg on repeated measures and this definition corresponds to a CTCAE grade 2 event [18,17]. CTCAE grade 1 hypertension is equivalent to pre-hypertension. In this study, a proteinuria event was defined as either 1+ proteinuria (CTCAE grade 1) on 3 consecutive recordings or CTCAE grade 2 (2+ proteinuria, 1.0-3.4 g /24 hours proteinuria or proten:creatinine ratio 0.5-1.9) or CTCAE grade 3 (≥3.5g /24hours proteinuria or protein:creatinine ratio > 1.9).

Analysis of the time and cumulative bevacizumab dose to first event for development of CTCAE ≥ grade 2 hypertension and proteinuria were performed.

3) Statistical analysis

Statistical analysis was performed using SPSS version 23 (IBM). A Kaplan-Meier analysis of time to first hypertension or proteinuria event was undertaken for patients who had completed 12, 24 and 36 months of follow-up respectively. Bivariate Pearson's correlations were used to examine correlations between baseline characteristics, initial dosing regime (5mg/kg two weekly or 7.5mg/kg three weekly),

cumulative bevacizumab dose, volumetric treatment response of the index tumour and the development of hypertension and proteinuria. An analysis of smoking history was performed with a binary grouping (current or previous smoker versus never having smoked).

Logistic regression models to identify predictors for the development of hypertension and proteinuria were subsequently performed using a Chi Square test of significance and Nagelkerke calculation of the R square statistic.

Longitudinal change in MAP and Cr Cl were assessed by analysis of marginal means over time.

Results:

The baseline characteristics of the cohort are shown in Table 1. The median follow-up and median duration of bevacizumab treatment were 32.7 months (range 12.0 – 60.2 months) and 27.4 months (range 3 - 58.6 months) respectively. Patients received an induction dose of 5mg/kg two weekly in 55/80 for a median of 6.9 months (range 3-41.7 months) and 7.5mg/kg three weekly in 25/80 for a median of 7.6 months (range 1.6-31.1 months); including 8 patients (6 patients on 5mg/kg two weekly and 2 patients on 7.5mg/kg three weekly) who did not drop to maintenance dose (2.5-5mg/kg 4 weekly) for the duration of their treatment at the discretion of their treating physician (median 15.9 months; range 3-42.7 months). The median total dose per kilogram was 166.25mg/kg (range 40 – 615 mg/kg).

There were 62 breaks in treatment in 41 patients with median treatment break duration of 3 months (range 1-15.5 months). This gave a corrected median duration of exposure to bevacizumab of 24 months (range 3-53.5 months). The reasons for breaks in treatment were adverse events in 24/62, surgical or dental procedures in 23/62, accidental injury in 7/62, non-response in 2/62, social in 4/62 and stable disease in 2/62. Twenty-one patients were followed up after cessation of treatment for a median duration of 10 months (range 2 – 19 months).

Adverse events

All of the adverse events recorded during treatment are summarised in Table 2. The most common adverse events were fatigue, hypertension and infection. A total of 580

events were recorded from 73 patients. There were no bevacizumab associated deaths. Breaks in treatment due to the development of either hypertension or proteinuria occurred in nine (11%) and six (7.5%) patients respectively. One patient developed significant left ventricular heart failure whilst on treatment and this case is described in detail below.

The Development of Hypertension and Proteinuria

During treatment and follow-up off treatment a total of 19/80 patients (24%) had at least one CTCAE grade 2 (18/80) or CTCAE grade 3 hypertension event (6/80) and 14/80 patients (17.5%) had a proteinuria event. A break in treatment (missing at least one dose) occurred due to a hypertension or proteinuria event in 9/19 and 6/14 of these patients respectively. Six additional patients had a CTCAE grade 1 hypertension event and 14 patients had a single 1+ proteinuria event. No grade 3 proteinuria events occurred.

Kaplan-Meier survival analyses for the development of grade 2 or 3 hypertension or proteinuria in patients who had completed 12, 24 and 36 months of follow-up are shown in Table 3. The survival curves for the development of hypertension or proteinuria to 24 months from start of treatment are shown in Figure 1.

The median time and dose per kg to first grade 2 or above hypertensive event were 2.7 months (range 0 - 33 months) and 30mg/kg (range 7.5 - 202.5 mg/kg) respectively.

The median time and dose to first proteinuria event were 10.7 months (range 3 - 36 months) and 85mg/kg (range 30 - 237.5 mg/kg) respectively.

Bivariate relationships with development of grade 2 or above hypertension were analysed and found age ($p<0.001$) and dosing regimen ($p=0.004$) to be significant. Logistic regression was then performed with hypertension as the dependent variable and age, gender, proteinuria and initial dose regime as predictor (independent) variables. The model Nagelkerke R square was 0.208, model p value < 0.001 with significant predictors being increasing age and initial dose regime. The rates of hypertension were 4% in the under 20 year old group, 16% in the 20-29 year old

group and 50% in the group ≥ 30 years old at the start of treatment. The number of patients per decade of age who developed hypertension is shown in Figure 2. Increased events were seen in the 7.5mg/kg three weekly group where 36% (10/25) developed hypertension compared to 16% (9/55) in the 5mg/kg two weekly group. Gender, genetic severity, smoking history, family history and total dose were not associated with the development of hypertension.

Proteinuria and hypertension co-existed in 7/14 patients but a correlation between hypertension and proteinuria did not reach statistical significance ($r=0.21$, $p=0.07$).

Only a family history of hypertension and a positive smoking history were found to be independent predictors of proteinuria on a logistic regression analysis with dependent variable proteinuria and independent variables age, smoking history, family history (Nagelkerke R square = 0.25, p value < 0.001).

Volumetric schwannoma response data was available in 46/80 patients [6]. In this subgroup no relationship was identified between volumetric imaging response and the development of either hypertension ($p=0.09$) or proteinuria ($p= 0.13$).

Hypertension and proteinuria after cessation of treatment

Twenty-one patients stopped treatment and were followed up for a median of 10 months (range 3-20 months) after their final dose of bevacizumab. This was elective discontinuation in 14/21 patients. Seven of 21 patients discontinued treatment due to an adverse event; 3 with proteinuria events; one each of infection, cardiac, creatinine elevation in the context of cyclophosphamide for a second condition and hepatobilary toxicity. These final four patients did not have hypertension or proteinuria throughout follow-up.

Two patients who stopped electively had developed hypertension during bevacizumab treatment and commenced anti-hypertensive medication. One of these patients (age 39 years) who completed 34 months of treatment remains on anti-hypertensive medication 8 months post treatment cessation. The second patient (age 27 years) who completed 23 months of bevacizumab treatment experienced a normalisation of their

blood pressure after cessation of treatment and was able to discontinue treatment with an anti-hypertensive agent at 9 months after cessation of bevacizumab.

In the remaining 12 patients who stopped treatment electively after a median of 35 months (range 12-60 months), there were no significant hypertension or proteinuria events during treatment or follow up after cessation of treatment.

Three patients ceased treatment due to proteinuria. One patient (age 11 years) had 12 months off treatment following a grade 2 proteinuria event. Before recommencing treatment for ongoing tumour growth the patient had 1+ proteinuria that occurred intermittently on re-treatment with bevacizumab. After a further 8 months of treatment with bevacizumab, 2+ proteinuria recurred although urinary protein:creatinine ratio was normal. The second patient (age 58 years) developed grade 2 proteinuria with an elevated albumin:creatinine ratio after 6 months of treatment. This patient had developed hypertension and commenced amlodipine after 1 month of treatment. At 9 months follow-up from cessation of bevacizumab (15 months after initial commencement of treatment), blood pressure was normal and the urine albumin:creatinine ratio had improved but remained elevated. The third patient (age 47 years) developed hypertension within the first month of treatment and commenced ramipril and amlodipine. After 17 months of treatment with bevacizumab, proteinuria developed with an elevated albumin:creatinine ratio and bevacizumab treatment was ceased. After 10 months off treatment proteinuria was no longer detected.

Modeling of mean arterial pressure and creatinine clearance over time

In all patients with available MAP from every cycle of treatment and 6 monthly creatinine clearance, linear modeling of mean arterial pressure (n=20) and creatinine clearance (n=62) over time did not show significant change in either measure over time.

Case of dilated cardiomyopathy presenting with palpitations and dizziness

A 19 year old male commenced treatment with bevacizumab for a growing left vestibular schwannoma at 5 mg/kg two weekly for 6 months then decreased to a maintenance dose of 5mg/kg four weekly. His history of NF2 included previous

resections of longitudinally extensive cervical spine ependymoma (C4 –T3) at ages 15 and 18, adjuvant radiotherapy to the ependymoma age 18 and deafness on the right secondary to a vestibular schwannoma (VS). After 15 months of bevacizumab treatment, the left VS was stable but the right VS continued to grow. Treatment was suspended for 6 months and the right VS resected and an Auditory Brainstem Implant (ABI) fitted; After a further 24 months of 5mg/kg four weekly bevacizumab (39 months from the initial start of treatment), treatment was ceased after an episode of palpitations and pallor. Electrocardiogram demonstrated left bundle branch block and echocardiogram demonstrated left ventricular dysfunction with an ejection fraction of less than 35% in the context of a previously normal echocardiogram prior to commencement of bevacizumab. He was commenced on bisoprolol, ramipril and spironolactone. A myocardial perfusion scan raised the possibility of filling defects in keeping with possible previous myocardial infarction but there was no evidence of reversible ischaemia. After 12 months off bevacizumab and whilst continuing bisoprolol and ramipril cardiac MRI demonstrated that all coronary territories were viable with no focal myocardial scarring or fibrosis and good left ventricular function. An echocardiogram 5 years after initially commencing bevacizumab and 20 months after cessation of bevacizumab showed low normal left ventricular ejection fraction. He has had no further palpitations or breathlessness and medications for heart failure are to be withdrawn. The patient never had a documented episode of hypertension and did not experience any other adverse events.

Discussion:

While the majority of bevacizumab toxicity events in NF2 patients are low grade, the risk of hypertension and proteinuria remains a concern in this population of young patients requiring prolonged treatment with bevacizumab. The persistence of an abnormal albumin:creatinine ratio in one of the patients nine months following treatment cessation implies long-term nephrotoxicity is a significant concern. Renal biopsy reports in patients with bevacizumab associated proteinuria are sparse but the most commonly described change is of glomerular thrombotic microangiopathic change [19]. As NF2 patients have a higher rate of hypertension than age matched controls, exposure to bevacizumab may further increase that risk and this may account for why rates are similar to older general oncology populations [16].

Hypertension in our cohort appears to be an early event that may be related to patient factors, particularly age, rather than total dose exposure. Conversely, proteinuria often occurs much later in disease course, and is not necessarily preceded by hypertension. This variation in timing of events may be due to the proposed mechanism of hypertension and proteinuria in VEGF inhibition. Hypertension is thought to be at least in part mediated by decreases in nitric oxide pathways while disruption of podocytes and increased glomerular permeability may lead to proteinuria [14]. As with previous reports in NF2, aside from age, conventional risk factors for hypertension were not identified as independent risk factors for hypertension in our cohort.

Slusarz et al.[15] utilized single blood pressure recordings from infusion records to track the development of hypertension in NF2 patients while treated with bevacizumab. This has a risk of over estimation of hypertension. We used diagnostic criteria according to NICE, AHA and CTCAE definitions that require documentation of hypertension on repeated measures. However, in addition, part of the increase in hypertension rate in their cohort (15/26 patients, 58%) in comparison to our group may be the use of higher doses throughout treatment. However, we identified a higher rate of hypertension when using a dose of 7.5mg/kg three weekly than 2/14 patients reported in the cohort described by Blakely et al [8]. Both our group and case reports from others have demonstrated a protocol including a reduction in dose density and frequency can continue to provide control over tumour size [6,7]. In a case described Farschtschi et al. a patient who developed hypertension (equivalent to CTCAE grade 3 definition) had a break from bevacizumab and then restarted at a lower dose of 2.5mg/kg three weekly had no further hypertension [7]. However, in a meta-analysis of non-NF2 studies suggesting an increased risk of proteinuria and hypertension with high versus low dose bevacizumab, doses of up to 7.5mg/kg per dose were all considered low dose [20]. Our finding of a correlation between dose intensity during the induction treatment phase and development of hypertension may be consistent with this.

Slusarz et al describe a sequential development of proteinuria from none to 3+ proteinuria. This was not observed in our cohort. Particularly 1+ proteinuria can

have multiple aetiologies and did not precede 2+ proteinuria in the majority of our cases.

Correlations between the development of hypertension and proteinuria have been described in the general oncology literature. These have not been replicated in our study or another previously described small NF2 cohort [15]. The size of the groups observed on bevacizumab with NF2 may have been too small to identify any relationship that may exist between the risk of these two events. The relationship between tumour response to treatment and development of hypertension or proteinuria has only been identified by some groups and not others.

Importantly, we describe the first reported case of left ventricular failure in a patient with NF2 treated with bevacizumab. This event is particularly notable due to young age, lack of hypertension or previous exposure to cardiotoxic drugs. Congestive heart failure (CHF) associated with bevacizumab has been described in other oncology settings at a rate of 2-4% in some breast cancer trials but not in retrospective review of over 6000 patients treated for colorectal cancer. Previous exposure to cardiotoxic drugs such as anthracyclines, or to radiation, has been suggested as the main predisposing factor rather than advancing age or other risk factors for development of CHF [21]. However, a VEGF inhibitor specific mechanism, particularly in the context of hypertension and potential vascular remodeling has been suggested [22]. Our case raises the possibility of a VEGF inhibition specific mechanism for the development of left ventricular failure in patients exposed to bevacizumab.

Our study has shown that further work is required to determine the optimal dosing regimes for NF2 patients receiving bevacizumab to minimise potentially serious toxicity without impacting on efficacy. Such strategies could potentially include a reduction in dose intensity during treatment induction and the consideration of lower maintenance does and drug holidays in patients who are likely to be on long-term treatment. While induction doses of 5mg/kg two weekly and 7.5mg three weekly have been previously viewed as equivalent, it may be necessary to reconsider this in light of the observed differences in hypertension rates observed.

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Acknowledgements:

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Patrick Axon, Neil Burnet, Neil Donnelly, Juliette Durie-Gair, Martin English, Nicola Folland, Fiona Harris, Frances Harris, David Heney, Anke Henseik, Sarah Jeffries, Richard Knight, Tamara Lamb, Robert Macfarlane, Richard Mannion, James Nicholson, Richard Price, Ella Rands, Paul Sanghera, Daniel Scoffings, Amy Taylor, James Tysome, *London:* Chris Hammond, Karine Lascelles, Charles Nduka, Terry

Nunn, Rupert Obholzer, Shakeel Saeed, Adam Shaw, Nick Thomas, Suki Thomson, Daniel Walsh, Victoria Williams, Sue Wood, *Manchester:* Raji Anup, Chris Duff, Simon R Freeman, Emma Howie, Susan M Huson, Nicola Jarvis, Ian Kamaly-Asi, Mark Kellett, Andrew King, John-Paul Kilday, Simon K Lloyd, Connor Malluci, Deborah Mawman, Sam Mills, Martin O'Driscoll, Sonia Patel, Mary Perry, Scott A Rutherford, Vilka Scott-Kitching, Stavros M Stivaros, Owen Thomas, Grace Vassallo, Charlotte L Ward, *Oxford and South West:* Lucy Cogswell, Louise Dalton, Caroline Dodridge, John Elston, Henk Giele, C Oliver Hanemann, Wendy Howard, David Johnson, Richard Kerr, Avianna Laws, James Lee, Elle Mace, Anne May, Chris Milford, Pieter Pretorius, James Ramsden, Carolyn Redman

Dr Morris is grateful for the support of an NIHR RCF grant from the University of Oxford. The funder had no role in the design or execution of the study.

Legends:

Figure 1: Kaplan-Meier analysis of hypertension (HTN) and proteinuria of n=55 patients 24 months from start of treatment

Figure 2: The patients per decade age group who developed hypertension (grade 2 or above) whilst on treatment with bevacizumab. Blue= no hypertension, Red = developed grade ≥2 hypertension.

Table 1: Baseline characteristics of cohort (n=80).

*One patient declined genetic testing, numbers rounded.

Table 2: The frequency of adverse events categorized by CTCAE grade. The % refers to the whole patient cohort (n=80) except for menstrual changes which are calculated as a proportion of female patients only (n=32). Blank cells denote no adverse event.

^ Previous background of depressive illness. Psychotic event thought to be secondary to this rather than bevacizumab exposure. *Seizure suspected to be secondary to infection rather than bevacizumab exposure.

Table 3: Survival proportions as a percentage of the study cohort available for analysis of hypertension and proteinuria end points at 12 (n=80), 24 (n=55) and 36 (n=36) months from start of treatment (Kaplan-Meier analysis).

Table 1:

Median age (range)	24.5 (11-66) years
Number of patients per age bracket	
<20 years	28
20-29 years	27
30-39 years	12
40-49 years	6
≥50 years	7
Gender M:F (% male)	48:32 (60%)
Median BMI (range)	23.3 (15.3-30.2) kg/m2
Family history of hypertension: n (%)	8 (10%)
Positive smoking history: n (%)	15 (19%)
Genetic severity (%)*	
Mild	25%
Moderate	30%
Severe	44%

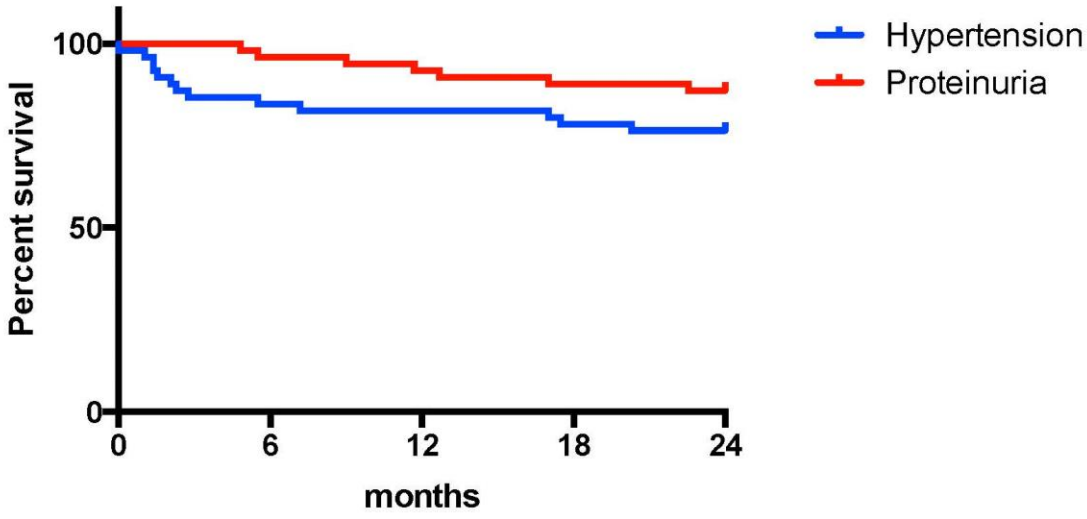
Table 2:

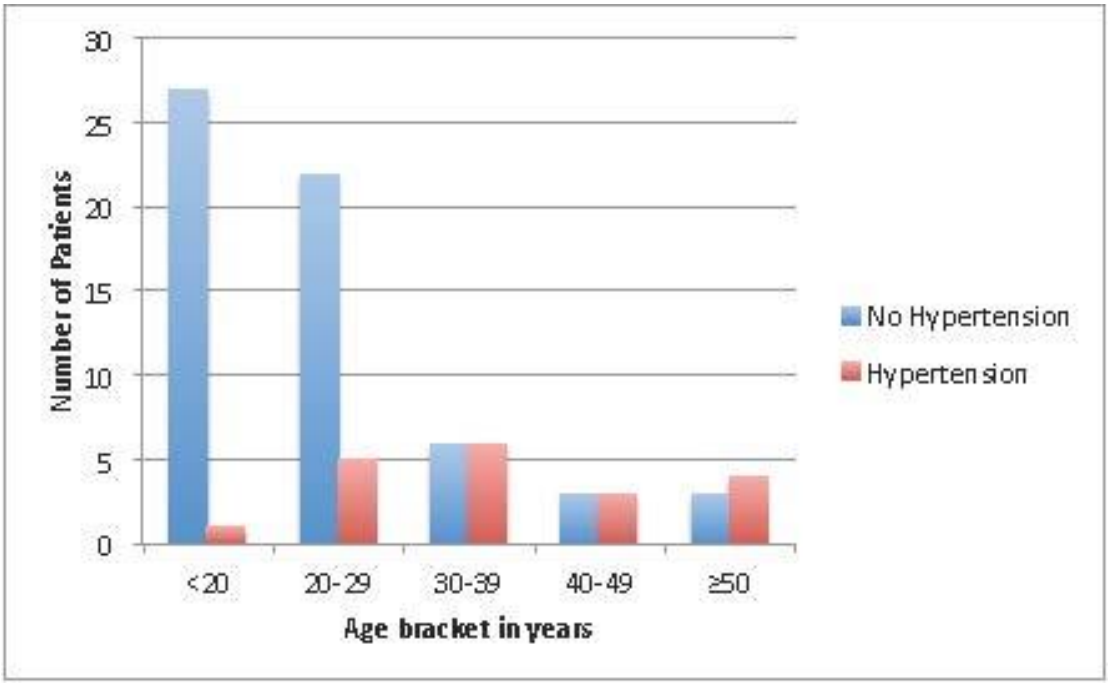
Adverse event	Grade 1			Grade 2			Grade 3			Grade 4		
	Events	Patients	% Cohort	Events	Patients	% Cohort	Events	Patients	% Cohort	Events	Patients	% Cohort
Hypertension	13	9	11%	32	18	23%	14	6	8%			
Infection	8	7	9%	44	16	20%	4	3	4%	2	2	3%
Proteinuria	62	28	35%	24	14	18%						
Fatigue	85	30	38%	15	9	11%	1	1	1%			
Pain	5	5	6%	9	7	9%						
Mucositis	40	16	20%	11	6	8%						
Nausea	33	14	18%	4	3	4%						
Menorrhagia	3	3	9%	3	3	9%	1	1	3%			
UTI				3	3	4%						
Constipation	9	6	8%	4	2	3%						
Rash	6	6	8%	2	2	3%	1	1	1%			
Ulceration	6	5	6%	4	2	3%						
Delayed wound healing	4	4	5%	2	2	3%	1	1	1%			
Hepatobiliary Disorder	4	3	4%	2	2	3%	1	1	1%			
Vomiting	5	3	4%	3	2	3%						
Diarrhoea	32	11	14%	1	1	1%						
Irregular Menses	8	6	19%	6	1	3%						
Depression	3	2	3%	1	1	1%				1	1	1%
Haematuria	3	2	3%	1	1	1%						
Hyperkalemia	4	2	3%	4	1	1%	1	1	1%			
Periodontal disease	4	2	3%	1	1	1%						
Arthralgia				2	1	1%						
Epistaxis	15	11	14%									
Headache	3	3	4%									

Rectal bleeding	3	3	4%									
Creatinine elevation	2	2	3%									
Dizziness	4	2	3%									
Haemoglobin (elevated)	4	1	1%									
Palpitations	1	1	1%									
Heart failure							1	1	1%			
Renal function change	1	1	1%									
Thrombocytopenia	1	1	1%							1	1	1%
Psychosis							1^	1	1%			
Seizure										1*	1	1%

Table 3:

	Survival proportions (%)		
	12 months	**24 months**	**36 months**
Hypertension	81%	76%	78%
Proteinuria	90%	87%	86%


Percent survival
100
50
0
0
6
12
18
24
months
Hypertension
Proteinuria


30
25
20
15
10
5
0
Number of Patients
<20
20-29
30-39
40-49
≥50
Age bracket in years
No Hypertension
Hypertension