PAPER 9

Title: Serum Metal Ion Concentrations in the Setting of an Oncologic Endoprosthesis: Is There Cause for Concern?

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Background: Multidisciplinary management consisting of surgery and chemotherapy has improved survival in patients with extremity bone sarcomas. Although chemotherapy is essential in survival, its use is associated with late complications including cardiomyopathy and renal failure. Limb salvage utilizing and endoprosthesis has become the primary means for reconstruction following oncologic resection. Endoprosthesis are commonly made of cobalt-chromium (CoCr) alloy and titanium (Ti) which can undergo wear and corrosion with release of Co, Cr and Ti ions into the surrounding tissue and blood. Elevated serum levels of Co and Cr are associated with cardiac, renal and neurotoxicity, and as such has the potential to potentiate renal and cardiac failure in this vulnerable population. Currently there is a paucity of data examining the serum concentration of these metal ions in patients with an endoprosthesis.

Purpose: The purpose of the current series was to 1) Evaluate the serum concentration of Co, Cr and Ti metal ions in patients with endoprosthesis.

Methods: Serum samples of Co, Cr and Ti were obtained from 24 (12 male:12 female) patients with a history of an endoprosthetic reconstruction of the lower extremity which was performed following an oncologic resection. The mean age at the time of surgery was 45±20 years and the mean time from surgery to the serum collection was 12±10 years. The most common diagnosis was osteosarcoma (n=11, 46%). Eighteen (75%) had a history of receiving chemotherapy which would impact cardiac or renal function. Implants included distal femoral replacements (n=15), proximal femoral replacement (n=7), proximal tibial replacement (n=1) and total femoral replacement (n=2).

Reference ranges for the serum values included Co and Cr < 1 ppb, Ti < 2 ppb. Risk stratification was based on the current American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, and The Hip Society recommendations for low (<3 ppb), moderate (3-10 ppb) and high (>10 ppb) risk patients.

Results: The Co levels were elevated in fifteen (63%) patients and Cr levels were elevated in 7 (35%), all patients with elevated CR also had elevated Co levels. In patients with elevated serum ion values, the mean Co level was 9.6(range 1.1-35) ppb and the mean Cr level was 5.9 (range 1.6-21.7) ppb. The Ti levels were elevated in 3 (13%) patients, with a mean level of 4 (range 3-5) ppb.

Based on the current recommendations for risk-stratification, 6 (25%) would be “low risk”, 4 (17%) would be “moderate risk” and 6 (25%) would be considered “high risk”. There was no difference in the time from implant placement to serum collection in patients with elevated serum metal ion values and those without elevated values (12±10 vs. 12±11 years, p=0.99). In addition, there was no difference in the time from implant placement to serum collection in patients with a low risk/normal or moderate/high risk groups (10±10 vs. 14±11 years, p=0.36).

In patients with elevated metal ion values 14 (88%) had a reconstruction utilizing a Stryker (Mahwah, New Jersey) GMRS implant, 1 (6%) Zimmer/Biomet (Warsaw, Indiana) OSS implant and 1 (6%) Depuy (Warsaw, Indiana) LPS. In patients without elevated levels, implants included Stryker GMRS (n=5, 63%), Depuy (Warsaw, Indiana) LPS (n=3, 37%).

Conclusion: In certain patients with a modular endoprosthesis serum metal ion values are elevated. Currently there is a lack of data to guide clinicians on if metal-ion levels should be checked on patients with these implants and if these elevations can impact the patient’s clinical outcome. The results of the current study indicate that Co levels were elevated in many of these patients, with over 40% of patients being at least “moderate risk” for

complications associated with their implant. Further studies are needed to determine if these ion levels change over time and if these serum ion levels lead to cardiac and renal complications.

Table 1: Patients Undergoing Endoprosthetic Reconstruction

Patient	Gender	Age at surgery	Type of procedure	Time from Surgery to Lab Draw	Cobalt Level (PPB)	Chromium Level (PPB)	Chemotherapy	Diagnosis
1	Male	57	DFR - GMRS	14 Years	3.3	2		Giant Cell Tumor
2	Male	55	PFR - GMRS	8 Years	2.7	<1	MAI	Osteosarcoma
3	Female	64	DFR - GMRS	8 Years	1.8	<1	AI	Synovial Sarcoma
4	Female	15	DFR-GMRS	25 Years	<1	<1	MAP	Osteosarcoma
5	Male	54	DFR- GMRS	4 Years	1.4	<1	R-CHOP	Lymphoma
6	Female	36	DFR – Biomet	4 Years	1.6	<1		Giant Cell Tumor
7	Female	53	DFR - GMRS	10 Years	<1	<1		Chondrosarcoma
8	Female	16	DFR - Howmedica	27 Years	<1	<1	MAP	Osteosarcoma
9	Female	53	DFR - GMRS	12 Years	5	<1	AI	Synovial Sarcoma
10	Female	62	PFR LPS	2 Years	<1	<1	CE	Metastatic Disease
11	Male	65	PFR LPS	1 Year	<1	<1	PA	Metastatic Disease
12	Male	66	PFR LPS	6 Months	1.1	<1		Metastatic Disease
13	Female	64	PFR - GMRS	24 Years	<1	<1		Plasmacytoma
14	Female	52	DFR GMRS	2 Years	12	1.6	MAP	Osteosarcoma
15	Male	16	DFR - GMRS	26 Years	10.8	3.9	MAP	Osteosarcoma
16	Female	33	Total Femur - GMRS	14 Years	16.7	4.9	MAI	Osteosarcoma
17	Male	19	DFR - Howmedica	33 Years	31.7	21.7	MAP	Osteosarcoma
18	Female	28	DFR-GMRS	27 Years	<1	3	AIE	Ewing Sarcoma
19	Male	62	PTR - GMRS	4 Years	14.9	<1	AP	Osteosarcoma
20	Male	64	DFR - GMRS	8 Years	4.8	<1		Parosteal Osteosarcoma
21	Male	16	DFR -GMRs	24 Years	1.7	<1	MAP	Osteosarcoma
22	Female	75	PFR - LPS	9 Months	<1	<1	D-RVd	Multiple Myeloma
23	Male	12	PFR - GMRS	7 Years	<1	<1	MAP	Osteosarcoma
24	Male	52	DFR - GMRS	4 Years	35	4.3	MAP	Pagets Sarcoma

*DFR: Distal Femoral Replacement; PFR: Proximal Femoral Replacement; PTR: Proximal Tibial Replacement; GMRS: Global Modular Replacement System (Stryker Orthopaedics; Mahwah, New Jersey, USA); LPS: Limb Preservation System (DePuy, Warsaw, Indiana, USA); MAI: Methotrexate, Adriamycin, Ifosfamide; AI: Adriamycin, Ifosfamide; MAP: Methotrexate, Adriamycin, Cisplatin; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin hydrochloride, Vincristine, Prednisone; CE: Cisplatin and Etoposide; PA: Pembrolizumab and Axitinib; AIE: Adriamycin, Ifosfamide, Etoposide; D-RVd: Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone