Chronic Ifosfamide and Cisplatin induced nephrotoxicity in a case of primary pulmonary synovial sarcoma

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ABSTRACT
Synovial sarcoma arising from the lungs and pleura is very uncommon and comprise only 0.5% of all primary lung malignancies and carries a very poor prognosis. Cisplatin and Ifosfamide, either alone or in combination, are the main chemotherapeutic agents; both are associated with both acute and chronic adverse effects on the kidneys. We report a rare case of poorly differentiated synovial sarcoma of lung, who was treated with these chemotherapeutic agents and developed chronic kidney disease stage 5, and presently on maintenance hemodialysis for the past 12 months.

Key word: Ifosfamide, Cisplatin, chronic kidney disease

INTRODUCTION
Ifosfamide is a synthetic analog of Cyclophosphamide that has been approved for concurrent use with other drugs (usually Cisplatin, Etoposide or Vinblastine) in the treatment of sarcomas and metastatic germ-cell testicular cancer. Nephrotoxicity due to direct tubular injury is a prominent complication of Ifosfamide therapy. In addition to tubular dysfunction, reduction in glomerular filtration rate is generally mild unless ifosfamide is given in combination with another nephrotoxin such as Cisplatin.

CASE REPORT
A 21 year male presented in December 2009 with hemoptysis, dull aching diffuse chest pain and progressive dyspnea of one month duration and bilateral multiple rounded lung parenchymal lesions on X ray chest (Figure 1a); he was diagnosed to have primary synovial sarcoma on histology (CT Guided Lung biopsy) and immunohistochemistry was positive for vimentin, B cell lymphoma - 2(Bcl-2), calretinin and CD 99. He was initially treated with chemotherapy [Adriamycin - 160mg plus Cisplatin 120mg (6 cycles) followed by Gemcitabine plus Docetaxel (3 cycles)] over a period of 9 months till September 2010. He had symptomatic relief and resolution of pulmonary lesions on X
Ray chest (figure 1b). In January 2011, he presented with right hemiparesis and MRI brain showed hemorrhagic lesions in the left frontal and parietal lobes, possibly due to metastasis and was treated with palliative radiotherapy (2000cGy in 5 divided doses). His renal functions were normal (serum creatinine 1.2mg/dl, urinalysis normal) and was discharged with partial improvement in neurologic status with an advice to continue physiotherapy as an outpatient. One month later, he was readmitted with hemoptysis, progressive dyspnea of 4 days duration, and X ray chest showed multiple nodular opacities (figure 2a) in both the lung fields; was diagnosed to have resolving of pulmonary synovial sarcoma. He was treated with Ifosfamide (1.5g/m2) plus Mesna (400mg) daily for 3 days in week (total 5 cycles over 7 weeks). The dose of Ifosfamide was increased by 20% (1.8 gm/m2) in 4th and 5th cycles as there was only minimal improvement in his symptoms and shadows on X ray chest. His symptoms had improved at the end of Ifosfamide chemotherapy. In May 2011, he presented with nausea, poor appetite, generalized weakness of two weeks duration to Nephrology OPD. Investigations showed minimal proteinuria (urine albumin +), glucosuria, and severe renal failure (serum creatinine 4.7 mg/dl, eGFR 16.8ml/min/1.73m2) and the subsequent cycles of chemotherapy were withheld, and the renal failure was managed conservatively. He was admitted with progressive fall in urine volume, uremic symptoms and worsening of serum creatinine to 9.6mg/dl, (eGFR 7.3ml/min/1.73m2). He was initiated on hemodialysis and renal biopsy was performed. Renal histology showed predominantly tubulointerstitial changes (simplification of the epithelium, interstitial edema and moderate lymphocytic and plasma cell interstitial infiltrates and interstitial fibrosis with tubular atrophy - 20%). Few tubules showed atypically enlarged tubular cells with great variation in size and shape of the nuclei, mostly with visible nucleoli (figure 2b). Glomeruli appear near normal in size andcellularity. Peripheral capillary loops, interlobular arteries and arterioles appear unremarkable. Hemodialysis was continued and he is dialysis dependant for the last 12 months.

**DISCUSSION**

Synovial sarcomas accounts for approximately 8% of soft tissue sarcomas (2). These tumors are not derived from the synovium, but from immature mesenchymal elements. They are divided into four histologic types: biphasic, monophasic fibrous, monophasic epithelial, and poorly differentiated. Our case was a poorly differentiated type. Diagnosis is made from histology, supplemented with immunohistochemistry (IHC) and cytogenetic studies. Immunohistochemically, synovial sarcomas are nearly uniformly positive for cytokeratin, EMA (Epithelial Membrane Antigen), (B cell lymphoma) Bcl-2, and vimentin, and negative for (Solubility in 100% dilution) S-100, desmin, smooth muscle actin, and vascular tumor markers (3). IHC studies in this case were positive for vimentin, Bcl-2, calretinin and CD 99. Cytogenetic studies of synovial sarcomas have revealed the chromosomal translocation t(x;18) (p11;q11). This translocation fuses the SYT gene from chromosome 18 to either of two homologous genes at Xp11, SSX1 or SSX2. SYT-SSX1 and SYT-SSX2 are thought to function as aberrant transcription regulators. The sensitivity of this test for diagnostic purposes approaches 100% (2).

Synovial sarcoma typically presents in adolescents and young adults (average age at presentation 25 yrs), most commonly in the soft tissues of the extremities, especially near large joints, but other sites like head and neck, lung, heart, mediastinum, and abdominal wall have been reported. Synovial sarcoma arising from the lungs and pleura have rarely been reported. Pulmonary sarcomas are very uncommon and comprise only 0.5% of all primary lung malignancies (4).

The prognosis for patients with pulmonary synovial sarcoma is poor, with an overall 5-year survival rate of 50%. Factors predicting a worse prognosis include tumor size (＞5 cm), male gender, older age (＞20 years), extensive tumor necrosis, high grade of malignancy, large number of mitotic figures (＞10 per 10 high-powered fields), neurovascular invasion, and, recently, the SYT-SSX1 variant (3). The main prognostic factor is the ability to achieve a complete resection. The prognosis for patients with the SYT-SSX2 abnormality is better (no deaths in the first 5 years after surgery in one study group) than that for patients with the SYT-SSX1 abnormality (4).

There is no standardized therapy; most patients are treated with surgery or with surgery and adjuvant radiation therapy. The rarity of this tumor has not permitted controlled studies on adjuvant chemotherapy. Synovial sarcomas are chemosensitive and the agents tried include Cisplatin, Ifosfamide, Doxorubicin, Gemcitabine and Docetaxel, with an overall response rate of approximately 24% (4).

Renal dysfunction related to treatment of synovial sarcoma

**Cisplatin**

Cisplatin is a common antineoplastic drug used for the treatment of solid tumors. Its chief dose limiting side effect is nephrotoxicity; 20% of patients receiving high-dose cisplatin have severe renal dysfunction (5). The kidney tissue accumulates Cisplatin to a greater degree (5 times the serum concentration) than other organs and is the major route for its excretion. However, conversion of Cisplatin to nephrotoxic molecules in the proximal tubule cells is necessary for cell injury. Cisplatin is conjugated to glutathione and then metabolized through a gamma glutamyl transpeptidase and a cysteine
Cyclophosphamide is converted to CAA. As CAA is to chloroacetaldehyde (CAA), whereas only 10% of their metabolism, toxicity, and therapeutic spectrum. Approximately 45% of the therapeutic dose of Ifosfamide is typically metabolized via N-dechloroethylation to chloroacetaldehyde (CAA), whereas only 10% of Cyclophosphamide is converted to CAA. As CAA is thought to induce neurotoxicity and nephrotoxicity, this is likely to account for the higher prevalence of these untoward events among patients treated with Ifosfamide. Specific toxicities related to Ifosfamide include hemorrhagic cystitis (caused by acrolein and can be prevented with mesna), neurotoxicity and nephrotoxicity7.

The incidence of renal toxicity varies between 5% and 30% and CAA is proposed to be the predominant nephrotoxin and mesna has no effect on it. Although renal damage is often acute and reversible, chronic toxicity may develop with potentially serious consequences. Proximal tubular dysfunction is the commonest presentation, and may lead to a Fanconi syndrome, including hypophosphataemic rickets and proximal renal tubular acidosis; although distal tubular impairment has been described, it is relatively rare9.

Several risk factors for the development of chronic nephrotoxicity have been described; total ifosfamide dose, age of the patient, previous or concurrent cisplatin treatment, and unilateral nephrectomy are the most important risk factors7. Brandis estimated the overall incidence of renal tubular dysfunction in patients treated with ifosfamide to vary between 10 and 20%, with only 1-3% of cases showing severe clinical symptoms.

Chronic renal failure due to ifosfamide is extremely rare and occurs in patients treated with very high doses (daily dosages >5 g/m2). There are no known measures to prevent ifosfamide renal toxicity8.

Because of the ongoing dispute and the lack of consensus on the best chemotherapeutic regimen, numerous ifosfamide regimens (both as monotherapy and in combination with others) have been tried in patients with soft tissue sarcomas. Monotherapy showed a response rate of 38% and median overall survival of 1 year. Several trials have been performed exploring the feasibility of ifosfamide-containing combinations and whether or not such combinations are more effective than single-drug regimens. The combinations studied are doxorubicin plus ifosfamide (high response rates of 50%–60%), four-drug combination CYVADIC (cyclophosphamide, vincristine, doxorubicin, and dacarbazine), ifosfamide plus paclitaxel and gemcitabine plus docetaxel7.

Nephrotoxicity can be documented few months after completion of ifosfamide treatment and sometimes renal functions may gradually worsen. Outcome varies between individual patients; but the overall prognosis remains poor. Several risk factors like total ifosfamide dose, age at treatment, previous or concurrent cisplatin treatment and unilateral nephrectomy predicts the outcome9.

CONCLUSION
Primary pulmonary synovial sarcoma is an extremely rare malignancy of the lungs and pleura which requires histology, IHC for the diagnosis and cytogenetic studies
for prognostication. The poor prognostic factors in our case were tumor size (>5 cm), male gender, poorly differentiated histology. The prior use of Cisplatin increased the risk of nephrotoxicity related to Ifosfamide and the use of mesna did not afford protection from nephrotoxicity. Chronic renal failure due to Ifosfamide is extremely rare and occurred in our patient although he received much lower dose (1.5-1.8g/m2) than that has been described in literature.

REFERENCES