

# Lethal toxicity of anticancer drugs in Xeroderma pigmentosum

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December 27, 2022

## Abstract

Xeroderma pigmentosum (XP) is a rare genodermatosis characterized by defective DNA repair, leading to hypersensitivity to ultraviolet (UV) sunlight and predisposes to various cutaneous and non-cutaneous malignancies. Platinum compounds are used against cutaneous cancers as concurrent chemoradiotherapy. But the XP gene polymorphism has a potential role in metabolism of these agents and their susceptibility. Here, we report a case of cutaneous squamous cell carcinoma in a patient with XP who had severe toxicity to chemotherapy. We also discuss other similar cases reported in literature of this entity, to highlight this potentially lethal pharmacogenomic association.

## Lethal toxicity of anticancer drugs in Xeroderma pigmentosum

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Text word count 815;

Abstract word count: 94;

Brief running title: DEBABRATA ET AL

Key words: Xeroderma pigmentosa, squamous cell carcinoma, Platinum compounds, adverse drug reactions

Tables: 1

Figures: 2

Abbreviations

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XP	Xeroderma pigmentosa
cSCC	Cutaneous squamous cell carcinoma
AUC	Area under curve

TLS trans-lesion DNA synthesis  
NER Nucleotide excision repair

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## ABSTRACT

Xeroderma pigmentosum (XP) is a rare genodermatosis characterized by defective DNA repair, leading to hypersensitivity to ultraviolet (UV) sunlight and predisposes to various cutaneous and non-cutaneous malignancies. Platinum compounds are used against cutaneous cancers as concurrent chemoradiotherapy. But the XP gene polymorphism has a potential role in metabolism of these agents and their susceptibility. Here, we report a case of cutaneous squamous cell carcinoma in a patient with XP who had severe toxicity to chemotherapy. We also discuss other similar cases reported in literature of this entity, to highlight this potentially lethal pharmacogenomic association.

## MAIN TEXT

### Introduction

Xeroderma pigmentosum (XP) is a rare genodermatosis characterized by defective DNA repair, leading to hypersensitivity to ultraviolet (UV) sunlight, resulting in symptoms involving eyes, skin and nervous system. It also predisposes to various cutaneous and non-cutaneous malignancies(1).

Polymorphism in the XP gene is also responsible for individual variations in susceptibility to chemotherapeutic agents(2). Although this theoretically puts xeroderma pigmentosum patients at increased susceptibility to DNA damages by anticancer drugs, literature describing the sensitivity to individual drugs is limited, owing to the rarity of XP itself. In this article, we report a case of cutaneous squamous cell carcinoma in a toddler with XP who had severe toxicity to chemotherapy. We also review the available literature for the same.

### Case details:

A 4year old female, known case of xeroderma pigmentosum diagnosed at 6 months of age, presented to us with history of multiple nodular swellings over the face for 3 months. On examination, she had diffused hypopigmented-hyperpigmented macules and dry skin over the whole body. There were five nodular lesions of variable size (maximum 3x3cm) over the face and a single actinic horn over the chin (Fig-1). She was developmentally normal and had a normal audiogram, but had extreme photophobia. Due to multifocal facial involvement excision was deferred by dermatologists and she underwent biopsy of the lesions.

Histopathology was suggestive of hyperkeratosis, acanthosis, papillomatosis along with keratin filled cysts and superficially invasive squamous cell carcinoma (cSCC), positive for cytokeratin and p53 (Fig-2). There was no lymphadenopathy or distant metastasis. She was labelled as high risk cSCC due to several risk features: location (face), size > 2cm and multiple lesions(3). A multidisciplinary discussion was done and it was decided to start neoadjuvant chemotherapy (NACT) for her, followed by delayed surgery and radiotherapy. Due to non-affordability of immunotherapy, platinum based NACT was started, based on the previously reported responses in several case reports in literature(4)(5)(6)(7)(8).

She was started on 3 weekly carboplatin (AUC=6) and paclitaxel (175mg/m<sup>2</sup>) regimen. On day 5 of chemotherapy she presented with vomiting, loose stool, poor oral acceptance, decreased urine output and excessive irritability. Laboratory investigations revealed profound metabolic acidosis (pH 7.1, HCO<sub>3</sub>=5.8 mEq/L). She also had deranged liver and kidney function tests along with coagulopathy (AST= 4328 IU/L, ALT= 3850 IU/L, urea= 112 mg/dL, creatinine= 2.1 mg/dL, INR=3.2). In view of acute liver and renal failure she was started on haemodialysis, blood component replacement and other supportive measures including mechanical ventilation. After 12 hrs of admission the child developed dystonic posturing, worsening sensorium and hemodynamic instability requiring multiple inotropes. The child ultimately succumbed to the illness.

### Discussion:

There is only limited literature for chemotherapy toxicity in XP patients, owing to its rarity. Sumiyoshi et al(9) reported 2 elderly patients with XP variant with mutations in *POLH* gene encoding DNA polymerase  $\eta$  that is involved in the trans-lesion DNA synthesis (TLS). Both developed severe toxicity with cisplatin involving liver, kidney, cochlea, gastrointestinal tract and bone marrow ultimately resulting in death. Carneiro et al(10) reported another lethal nephrotoxicity following cisplatin in a young oral squamous cell carcinoma patient with XP. Gilbar et al(11) reported a similar toxicity with cisplatin in a patient who seems to be the only patient that survived the fatal toxicity. Both the later authors postulated the defective XPC gene to be the underlying genetic defects in these 2 patients. Our index case is the first such toxicity reported after carboplatin as per the current literature (Table-1).

XP is characterized by defective nucleotide excision repair (NER) pathway, that leads to excessive DNA damage by UV radiation. Booton et al(12) found that polymorphism in XPD gene is associated with platinum toxicity in lung cancer patients. Though in their cohort none had XP, this observation highlights the pharmacogenomic interaction involving the XP gene expression and platinum chemotherapy.

Platinum-DNA adduct formation is an important mechanism of its antineoplastic activity(13). Repair of these adducts occurs by NER, involving genes like XPA, XPB, and ERCC1-XPF(14). Recent in-vitro models suggest that XPC gene expression increases susceptibility of colorectal cancer cell lines to chemotherapy(15) and XPC mutations in fibroblasts increases oxidative DNA damage(16). In most of the XP subtypes one of the above loci are constitutionally defective and non-neoplastic cells are also at risk of exaggerated DNA damage by Platinum compounds, leading to toxicity.

Although the genetic subtype of the index case is not known, due to complete absence of neurological symptoms she was clinically labelled as XPC. Current evidence is insufficient to conclude if one or the other XP subtype is associated with more severe toxicity to chemotherapy. Also, it is not known whether similar toxicity is observed with anticancer drugs other than platinum compounds. In vitro studies of cells of various subtypes of XP can shed more light into their relative susceptibility to anticancer agents. In conclusion, we would recommend to withheld platinum compounds in XP patients and to closely monitor for toxicity of other anticancer drugs if at all used.

**Conflict of Interest statement:** The authors declare no conflict of interest.

**Acknowledgement:** We sincerely acknowledge the family of the patient for giving us the consent to publish the case

**Funding:** None

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**Legends:**

*Table 1:* Reported cases of toxicity to chemotherapy agents in Xeroderma Pigmentosa in literature.

*Figure 1:* Clinical photograph of the patient showing five nodular lesions of variable size (maximum 3x3cm) over the face and a single actinic horn over the chin

*Figure 2:* Biopsy of the lesion shows a squamous cell carcinoma (HE, 20x) with infiltrative borders (HE, 100x) and nuclear stypis (HE, 400x). Strong 53 staining is present (IHC, 100x)

Table 1: Reported cases of toxicity to chemotherapy agents in Xeroderma Pigmentosa in literature.

Author, year	Age/sex	Site	Additional therapy	Chemotherapy drug	Toxicity	Outcome
Sumiyoshi et al, 2017(9)	70y/f	Lung adenocarcinoma	Right lower lobe resection	CDDP 80 mg/m2 Vinorelbine 25 mg/m2	Diarrhea, ototoxicity, AKI, hepatotoxicity, myelosuppression	Death

Author, year	Age/sex	Site	Additional therapy	Chemotherapy drug	Toxicity	Outcome
	70y/m	Esophageal squamous cell carcinoma	Subtotal esophagectomy	CDDP 80 mg/m2 5-FU 800 mg/m2/day	Diarrhea, ototoxicity, AKI, hepatotoxicity, myelosuppression	Death
Carneiro et al 2019(10)	23y/f	Oral squamous cell carcinoma	Surgery and radiotherapy	CDDP 40 mg/m2	Diarrhea, AKI,	Death
Gilbar et al 2021(11)	42y/m	Neck cutaneous squamous cell carcinoma	Surgery and radiotherapy	CDDP 40 mg/m2	AKI	Improved
Index case	4y/f	Facial cutaneous squamous cell carcinoma	None	Paclitaxel 175 mg/m2 Carboplatin at AUC 6	Diarrhea, AKI, hepatotoxicity	Death

Figure 1: Clinical photograph of the patient showing five nodular lesions of variable size (maximum 3x3cm) over the face and a single actinic horn over the chin



Figure 2: Biopsy of one of the lesion shows (A) a squamous cell carcinoma (HE, 20x) with (B) infiltrative borders (HE, 100x) and (C) nuclear stypis (HE, 400x). (D) Strong p53 staining is present (IHC, 100x)





