Short Communications (NS-2)

CUTANEOUS SIDE EFFECTS OF SOME CHEMOTHERAPEUTIC AGENTS IN THE MALE ALBINO RAT (*Rattus norvegicus*)

Sastry M.S.*, Gotmare V.V., Dighade S. W. and Kashmiri Z.N.
Department of Zoology, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (INDIA)

Received July 05, 2012 Accepted November 20, 2012

ABSTRACT

Antineoplastic chemotherapies are widely used in many therapeutic protocols and are responsible for numerous cutaneous side effects. Much of the information recorded in the present study came from a decade study while studying the effects of some chemotherapeutic agents such as alkylating agents (cisplatin, carboplatin, oxaliplatin and cyclophosphamide); antimetabolite (methotrexate); plant alkaloids (vincristine and etoposide); anthracycline antibiotic (doxorubicin) on the male reproductive system and thyroid gland of rats. Some distinctive cutaneous side effects recorded were alopecia, hyperpigmentation, hypersensitivity reactions, photosensitivity, phlebitis, injection site reaction and thick dry skin, dryness, brittleness and ruffleness of hairs, nail changes, erythema, nail loss, pruritus (skin rash), ulceration, wound infection, skin necrosis, itching and allergic reaction. These side effects were dose and duration dependent and occurred in varying degree of frequency and severity with each class of chemotherapeutic drugs. Such studies would be useful to dermatologist, oncologist and in clinical management of oncology patients.

Key Words : Chemotherapeutic agents, Alopecia, Hyper pigmentation, Hypersensitivity

INTRODUCTION

Chemotherapeutic agents generally target rapidly dividing cells and consequently are toxic to organ systems with high metabolic rates, such as hairs, nails and skin. Much of our information on these cutaneous side effects comes from a decade study in this laboratory on various chemotherapeutic drugs while studying the adverse effect on the male reproductive system and thyroid gland. Understanding the cutaneous side effects will assist the dermatologist and oncologist to recognize them early and intervene before major problems occur. It would also be essential to pharmacists involved in the clinical management of oncology patients.

MATERIAL AND METHODS

Drugs

Alkylating agents (cisplatin, carboplatin, oxaliplatin, cyclophosphamide), antimetabolite (methotrexate), plant alkaloids (vincristine, etoposide), anthracycline antibiotic (doxorubicin).

Animals

For the present study healthy male Wistar strain albino rats weighing 281.67±6.01-276.00±3.06 g were obtained from the breeding colony of Department of Biochemistry, RTM Nagpur University, Nagpur, India were raised on a commercial pellet diet (Hindustan Liver Ltd.) and water Adlibitum. The animals were housed at constant temperature (28±2ºC) and relative humidity (60±10%) with a 12h light 12h dark cycle.

Treatments

Various sets of experiments were performed for each drug and were compared with the vehicle-treated control. The drug was administered intraperitoneally. The doses used are summarized in Table 1.

RESULTS AND DISCUSSION

The most commonly described effects in the present studies were skin adnexes, especially
hair with alopecia and hyper-pigmentation. These reactions occurred in varying degrees of frequency and severity with each class of chemotherapeutic drugs. Alopecia was the most commonly recorded effect for all the drugs with both the doses however more prominent with the high doses. The hair fall was more on the dorsal side with most of the drugs however with methotrexate the hair loss was temporary sometimes the hair loss was partial (methotrexate, cyclophosphamide, carboplatin). Hyper-pigmentation was very common with all the drugs studied in the present study but was generalized with cyclophosphamide and etoposide, figurated with methotrexate, vincristine and doxorubicin or localized with cisplatin, carboplatin and oxaliplatin, however, reactivity was less common with carboplatin, oxaliplatin and doxorubicin. In some -methotrexate treated animals horizontal hyperpigmented bands alternating with white hairs were also evident. The hyper-pigmented animals were with symptoms of weakness, weight loss and diarrhea. Hyper-pigmentation of nails (dark coffee color) has been observed with platinum compound, nitrogen mustard, cyclophosphamide and doxorubicin. A local congestion or redness of the skin or erythema was another cutaneous side effect which was specific to cisplatin, cyclophosphamide and vincristine. Nail loss was observed with etoposide. Allergic reaction was also observed with methotrexate. Hypersensitivity reactions were most commonly caused by doxorubicin, vincristine and platinum compounds cisplatin and carboplatin. Most of these reactions (pain/redness/swelling) were limited to the site of injection which vanished within 30-90 minutes. Red streaks along injection sites were also observed in cyclophosphamide treated animals. Doxorubicin (adriamycin), a potent intercalating antineoplastic agent caused severe local skin ulceration toxicity when the drug was extravasated during administration. Methotrexate and vincristine were associated with photosensitivity. Apart from above reactions pruritus (skin rash), wound-infection, dryness of the skin, brittleness and ruffleness of the hairs, skin necrosis, itching, and phlebitis were also noticed with most of the drugs used in the present study. Similarly unusual bleeding or brushing were observed with cisplatin. Over the recent decades, the dermatological complications of cancer chemotherapy have become an increasingly significant subject.

Alopecia was the commonest effect observed with all the drugs and also consistent to the other studies. The hair loss was found to be dose, drug and duration dependent. The dermatological side effects concerned with hyperpigmentation were also very much prevalent and specific to chemotherapeutic drugs used in the present study as described in the literature by.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Doses and Duration (mg/kg BW/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>4 and 10 mg for 30 days, 15 mg for 15 days</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>5 and 10 mg for 15 days</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>2.5 and 5 mg for 15 days</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>5.7 and 10 mg for 15 days, 100 mg as a single dose once in a week</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>3 and 6 mg for 15 days</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.06 and 0.12 mg for 30 days</td>
</tr>
<tr>
<td>Etoposide</td>
<td>10 mg for 15 days and 30 mg for 30 days</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>5 mg for 15 days, 2 mg for 30 days and 1 mg for 40 days</td>
</tr>
</tbody>
</table>

B.W. = Body weight
The ulceration and dermatomyositis observed with doxorubicin were perhaps due to long term administration. Out of eight drugs studied methotrexate and vincristine were commonly associated with photosensitivity and our results are comparable.

In the present study carboplatin, cyclophosphamide, etoposide and vincristine produced different allergic skin reactions such as pruritus, purpura, rashes and itching. The allergiers etions were also edema, phlebitis and erythema which varied in their symptoms depending upon the type of drug. Such allergic skin reactions have been described. Similarly in the present study hypersensitivity reactions were most commonly caused by platinum compounds, vincristine and doxorubicin were in accordance with observations of Hyperpigmentation (dark coffee color) of nails have been observed with platinum compounds, nitrogen mustards, cyclophosphamide and doxorubicin. Nail loss observed with etoposide. Similarly nail changes were observed with other drugs such as docetaxel.

CONCLUSION

From the foregoing studies it is concluded that these side effects were dose and duration dependent and occurred in varying degree of frequency and severity with each class of chemotherapeutic agents. Such studies would be useful to dermatologist, oncologist and in clinical management of oncology patients.

REFERENCES