Chemotherapy and radiotherapy for advanced testicular non-seminoma

1. The influence of sequence and timing of drugs and radiation on the appearance of normal tissue damage

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Summary

Acute and delayed normal tissue damage has been investigated in 63 advanced stage testicular non-seminoma patients receiving elective involved-field irradiation after chemotherapy and in 53 patients who had chemotherapy given for relapse after prior irradiation. The risk of death from complications due to chemotherapy was 0% and 9.4% (p < 0.025) in the two groups respectively. Gastro-intestinal damage and/or subcutaneous fibrosis was present in 12.6% and 24.5% of patients respectively, although only three patients have serious persisting disability. In patients receiving 35-45 Gy to the retroperitoneum the incidence of normal tissue damage was 0% and 25% (p < 0.001), respectively. In addition to the sequence in which chemotherapy and radiotherapy was delivered, the time interval between completion of radiotherapy and start of chemotherapy was important with 6/6 patients receiving drugs within 2 months of irradiation developing fibrosis. Abdominal surgery appeared not to influence the risk of damage. Of nine patients receiving drugs after infra-diaphragmatic and supra-diaphragmatic irradiation two died of neutropenic sepsis.

Introduction

Between 1976 and 1981, 63 patients with advanced testicular non-seminoma were treated by four to six cycles of chemotherapy consisting of vinblastine and bleomycin [10]. cis-Platinum, vinblastine and bleomycin [4] or bleomycin, etoposide and cis-platinum [7] followed 4 to 6 weeks later by irradiation of initial disease sites. During the same period 53 patients relapsing after radiotherapy received chemotherapy, the intervals between the end of irradiation and initiation of chemotherapy ranging...
from 0 to 156 months. The results of treatment are analysed separately [3]. It is the purpose of this report to present details of the acute and delayed complications of combined chemo-radiotherapy in an attempt to shed light on the significance for normal tissue tolerance of the sequence in which drugs and radiation are given and the time elapsing between irradiation and subsequent chemotherapy.

**Patients and methods**

**Staging protocol**

Staging included lymphography, CT scanning of the lungs and abdomen, ultrasonic scanning of the liver and retroperitoneum, intravenous urography, measurement of renal clearance, liver function tests and measurement of serum alpha-feto protein (AFP) and beta human chorionic gonadotrophin (HCG) levels.

**Staging classification**

The Royal Marsden Hospital staging classification was employed:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage I</th>
<th>Stage IM</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Abdominal status</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No metastases evident outside testis</td>
<td>No metastases</td>
<td>No clinical evidence of metastases but persistent elevation of serum AFP and/or HCG levels after orchiectomy</td>
<td>Infra-diaphragmatic nodal metastases</td>
<td>Supra-diaphragmatic nodal metastases</td>
<td>0 = negative lymphogram, A, B, C as for Stage II</td>
</tr>
<tr>
<td>II A</td>
<td>Metastases &lt; 2 cm diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II B</td>
<td>Metastases 2-5 cm diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II C</td>
<td>Metastases &gt; 5 cm diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVL 1</td>
<td>Extranodal metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVL 2</td>
<td>Multiple small pulmonary metastases &lt; 2 cm diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVL 3</td>
<td>Multiple pulmonary metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVH +</td>
<td>One or more &gt; 2 cm diameter</td>
<td></td>
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</tbody>
</table>

Abdominal status as for Stage II

*Small volume disease.* This category includes patients with Stage IM, IIA, IIB, IIC, IIIA, IIIB and IVA, B L 1 L 2.

*Large volume disease* includes patients with Stage IIC, IIIC, IVCL 1, IVCL 2, IVA, B or C L 3 and IVH + disease.

*Patients receiving chemotherapy followed by radiotherapy*

There were 63 patients in this group treated between 1976 and 1981. Their stage distribution was as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Count</th>
<th>Stage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>3</td>
<td>IVCL 1</td>
<td>5</td>
</tr>
<tr>
<td>IIB</td>
<td>8</td>
<td>IVBL 2</td>
<td>2</td>
</tr>
<tr>
<td>IIC</td>
<td>18</td>
<td>IVCL 2</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>IVL 3</td>
<td>1</td>
</tr>
<tr>
<td>IVAL 1</td>
<td>5</td>
<td>IVCL 3</td>
<td>1</td>
</tr>
<tr>
<td>IVBL 1</td>
<td>4</td>
<td>IVH +</td>
<td>2</td>
</tr>
</tbody>
</table>

Following four to six cycles of chemotherapy, patients were reassessed. Criteria for the use of radiotherapy included normalisation of serum markers and lack of progression of the initial extent of disease. Radiotherapy was given by 6 or 8 MeV photons anterior and posterior fields being used to treat the para-aortic ± pelvic node areas and in some patients the supra-diaphragmatic nodes ± a limited number of lung metastases. A tumour dose of 40–50 Gy was given with daily 2 Gy fractions over 4 to 5 weeks.

One to 2 months after surgery patients were considered for surgery if residual masses were present. Of the total group 23 came to surgery.

*Patients treated by chemotherapy for disease relapsing after radiotherapy*

Over the same period 53 patients were seen who
had had prior irradiation and who had relapsed. They were re-staged and their stages at relapse were as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>IIA</td>
<td>3</td>
</tr>
<tr>
<td>IIB</td>
<td>2</td>
</tr>
<tr>
<td>IIC</td>
<td>9</td>
</tr>
<tr>
<td>IVAL1</td>
<td>7</td>
</tr>
<tr>
<td>IVBL1</td>
<td>1</td>
</tr>
<tr>
<td>IVCL1</td>
<td>5</td>
</tr>
<tr>
<td>IVAL2</td>
<td>6</td>
</tr>
<tr>
<td>IVBL2</td>
<td>2</td>
</tr>
<tr>
<td>IVCL2</td>
<td>1</td>
</tr>
<tr>
<td>IVCL3</td>
<td>7</td>
</tr>
<tr>
<td>IVCL1</td>
<td>3</td>
</tr>
<tr>
<td>IVH+</td>
<td>2</td>
</tr>
</tbody>
</table>

The interval between the end of radiotherapy and start of chemotherapy ranged from 0–156 months. The tumour dose given varied from 12 to 56 Gy and treatment was given either with $^{60}$Co $\gamma$-rays or linear accelerator. Chemotherapy consisted of one of the combinations indicated above. Only six of this group came to surgery.

**Scoring of normal tissue damage**

The presence or absence, and if present the degree of subcutaneous fibrosis in the anterior abdominal wall and groin, was scored by three independent observers using a four point scale, (1) no abnormality, (2) mild fibrosis, (3) moderate fibrosis and (4) severe fibrosis.

Of the surviving 96 patients 24 were unavailable for scoring but since an effort had been made to record fibrosis in the patients’ notes during regular follow-up visits, this information was considered adequate for inclusion in the analysis. A note was made of continued bowel disturbance and surgery for bowel damage.

**Results**

As reported elsewhere [3] of the total group of 116 patients, 96 (82.7%) are alive and disease-free; 58/63 (92.1%) in the chemotherapy–radiotherapy group and 38/53 (71.7%) in those receiving chemotherapy after irradiation.

**Patients receiving chemotherapy before irradiation**

Patients managed with this protocol are considered in relation to the radiation dose delivered to the tumour bearing area.

(a) Tumour dose < 35 Gy. There were no patients in this group.

(b) Tumour dose 35–45 Gy. Of the 46 men in this group there was one post-operative death and two patients received chemotherapy for relapse after irradiation. These are analysed separately. Of the 43 patients at risk for developing normal tissue damage, three died of tumour at 12, 20 and 21 months. No patient in this group developed gastro-intestinal damage or subcutaneous fibrosis.

(c) Tumour dose > 45 Gy. Of 17 men in this group, two had chemotherapy for relapse after irradiation and have been analysed separately. Of the remaining 15 patients, three developed subcutaneous fibrosis and one gastro-intestinal damage and fibrosis. One patient with fibrosis has partial cord damage.

The case histories of the two latter patients are summarised below:

**Patient 1. (Stage IIIA, malignant teratoma undifferentiated, left orchidectomy, July 1976).** This patient received a single fraction of 3 Gy to the para-aortic and left pelvic nodes prior to chemotherapy which consisted of cyclophosphamide (2 g i.v.) and two cycles of vinblastine and bleomycin. One month after the second cycle of vinblastine and bleomycin he started radiotherapy (6 MeV photons) to an inverted Y field employing anterior and posterior fields and delivering a mid plane dose of 40 Gy in 22 fractions over 32 days. This was followed by a boost to the upper para-aortic nodes of 10 Gy in six fractions over 11 days. One month after completion of infra-diaphragmatic irradiation he received 41 Gy mid plane dose to the mediastinum and 47 Gy to the right neck in 29 days. One month later a residual retroperitoneal mass was excised which showed fibrosis only. Two months after surgery the patient developed herpes zoster of the right leg involving L4 and L5 dermatomes. He sub-
sequently developed weakness of the right leg which was considered to be due to zoster. Marked subcutaneous fibrosis within the radiation field in the anterior abdominal wall was documented 29 months after completion of radiotherapy. Thirty-eight months after radiotherapy he developed weakness of the left leg which deteriorated then stabilised. Six years after irradiation he is well and tumour free with bilateral leg weakness which is stable and which is attributed to radiation myelitis. In view of the dose of radiation delivered the normal tissue sequelae are perfectly consistent with radiation damage per se without postulating an exacerbation by chemotherapy.

Patient 2. (Stage IVCL₂, malignant teratoma undifferentiated, right orchidectomy December, 1976). This patient was treated with three cycles of vinblastine and bleomycin followed one month later by irradiation of the para-aortic nodes (50 Gy in 24 fractions over 39 days using 8 MeV photons). Twenty-seven months after irradiation he underwent a laparotomy for what was diagnosed as acute appendicitis. He was found to have mesenteric artery thrombosis with an area of gangrenous terminal ileum. The histological appearances were those of radiation enteritis. Six years after treatment he is tumour free but has mild persistent diarrhoea and steatorrhoea.

Patients treated with the sequential drug-radiation protocol and requiring further chemotherapy

Of three patients in this category two developed subcutaneous fibrosis.

Patients treated with chemotherapy after prior irradiation

(a) Tumour dose <35 Gy. There were four patients in this group, three are well but the fourth died of bleomycin lung toxicity.
(b) Tumour dose 35-45 Gy. Of 44 patients, three died of chemotherapy-induced neutropenic sepsis, one of chemotherapy-related gastro-intestinal haemorrhage and seven of tumour.

Eight patients developed subcutaneous fibrosis, one of whom died and two patients have gastro-intestinal damage. Their case histories are summarised below:

Patient 1. (Stage I, malignant teratoma intermediate, right orchidectomy March 1977). In this patient the radiotherapy details were as follows: irradiation to para-aortic and ipsilateral pelvic nodes, 40 Gy mid plane dose in 55 days using ⁶⁰Co γ-rays. Nine months after irradiation the patient relapsed and was treated with vinblastine and bleomycin (four cycles). Three months later he underwent laparotomy with resection of a loop of radiation damaged terminal ileum. Fifty-eight months after irradiation the patient has persisting bowel problems, weight loss and diarrhoea. However, interpretation of his clinical state is complicated by the fact that he developed thyrotoxicosis for which he is receiving carbimazole.

Patient 2. (Stage I, seminoma left testis 1969 Stage III, combined seminoma/teratoma right testis 1979). In 1969 the patient received radiotherapy to the para-aortic and pelvic nodes (44 Gy) with ⁶⁰Co γ-rays. Eleven years later he was treated with cis-platinum, vinblastine and bleomycin for metastatic non-seminoma following removal of the right testis. After the first cycle of chemotherapy he developed septicaemic shock, renal failure and paralytic ileus. After he had recovered he continued with three cycles of etoposide and cis-platinum. Since completion of treatment he has had persistent intestinal hurry with bouts of diarrhoea. Barium studies confirmed a shortened bowel transit time. Two years after completing chemotherapy he is tumour free, well and maintaining his weight although he still has occasional diarrhoea.

(c) Tumour dose > 45 Gy. Of five patients in this category one died of chemotherapy-induced neutropenic sepsis and one of tumour. Three patients developed subcutaneous fibrosis, one of whom died of uncontrolled malignancy.
Chemotherapy before radiotherapy

Radiotherapy before chemotherapy

% patients

Death from tumour
Post-operative death (Ch → Rt Group)
Myocardial infarct (Rt → Ch Group)
Subcutaneous fibrosis and/or gastrointestinal damage
Chemotherapy-related deaths

Fig. 1. Advanced non-seminomatous germ cell testicular tumours: Tumour deaths and complications in patients receiving chemotherapy before or after radiotherapy (Royal Marsden Hospital, 1975-1981).

Influence of the order in which chemotherapy and radiotherapy are given

As shown in Fig. 1, there is a lower mortality from disease in patients receiving chemotherapy before irradiation (6.3%) compared with those who received chemotherapy after irradiation (15.1%). The mortality from chemotherapy-related complications (0% and 9.4%, respectively) (p < 0.025) and the incidence of subcutaneous fibrosis and/or bowel damage (12.6% and 24.5%, respectively) (not significant) shows a similar trend.

Figure 2 shows an analysis of normal tissue sequelae in relation to radiation dose. This shows that normal tissue damage only occurred in patients receiving radiotherapy after chemotherapy when the tumour dose was > 45 Gy in contrast to the finding that ten patients receiving 35-45 Gy prior to chemotherapy subsequently developed subcutaneous fibrosis or gastro-intestinal damage.

Influence of time interval elapsing between radiotherapy and chemotherapy in patients treated for tumour relapse after irradiation

As shown in Fig. 3, there is a striking relationship between sequence and timing and risk of normal tissue damage. In order to examine the possible influence of the interaction of drugs and radiation per se on normal tissues only patients receiving radiation doses in the 35-45 Gy range have been included. Of 43 patients receiving chemotherapy prior to irradiation none had complications whereas 6/6 exposed to chemotherapy within 2 months of the completion of irradiation have developed subcutaneous fibrosis or gastro-intestinal damage. At longer intervals the risk of complications was reduced although even in patients treated 6 months or more after irradiation there appeared to be an increased risk of normal tissue damage.

Influence of surgery on appearance of normal tissue damage

Figure 4 summarises the development of fibrosis and/or bowel damage in relation to radiation dose, presence or absence of abdominal surgery and timing of chemotherapy in relation to irradiation. Surgery appeared to play no role in the development of normal tissue sequelae. In fact, complications appearing in patients receiving 35-45 Gy prior to chemotherapy occurred predominantly in patients who had not been submitted to surgery.

Acute drug-related deaths and extent of radiation fields

As shown in Fig. 5, patients who had received infra-diaphragmatic and supra-diaphragmatic irradiation were at increased risk from severe chemotherapy-related complications resulting in death with 2/9 patients dying of neutropenic sepsis.
Fig. 2. Advanced non-seminomatous germ cell testicular tumours: Complications in patients receiving chemotherapy before or after radiotherapy (Royal Marsden Hospital, 1976-1981).

Fig. 3. Influence of sequence and timing of chemotherapy and radiotherapy on the risk of normal tissue damage in patients treated for advanced testicular non-seminoma (Royal Marsden Hospital, 1976-1981).

Fig. 4. Advanced non-seminomatous germ cell testicular tumours: Complications in patients treated with radiotherapy and chemotherapy in relation to surgery (Royal Marsden Hospital, 1976-1981).
as shown in Fig. 6, nine patients were judged to have moderate or severe complications. In fact, of the entire group only three have serious sequelae, the details of these patients are summarised in the case histories above.

**Time to appearance of subcutaneous fibrosis or bowel damage**

As shown in Fig. 7, 80% of complications became clinically evident by one year after the completion of chemotherapy. In patients receiving drugs soon after irradiation normal tissue complications sometimes developed extremely rapidly.

**Discussion**

The observations made in the two groups of patients in this study indicate that, in the particular clinical situation under consideration, radiotherapy after chemotherapy is associated with significantly less toxicity than the converse sequence. Thus, there was a 9.7% overall complication rate in the drug-radiation group compared with 33.9% in the radiation-drug group ($p < 0.001$). When only patients receiving 35-45 Gy are considered the difference is more striking with 0/47 men in the drug-radiation treatment group developing subcutaneous fibrosis or bowel damage compared with 13/40 in the radiation-drug group ($p < 0.001$). These results demonstrate that with the drug combinations used in the treatment of testicular non-seminoma and with radiation dose levels in the 35-45 Gy range, sequential drug-radiation therapy can be delivered safely. Problems arose only when tolerance levels
of radiation (> 45 Gy) were exceeded. On the basis of these observations it is concluded that there is no evidence of modification by prior chemotherapy of normal tissue responses to radiation doses in the range 35-45 Gy.

It is clear that the delivery of chemotherapy after radiotherapy is associated with more acute normal tissue damage particularly neutropenia. Thus, whereas there were no deaths in the drug-radiotherapy group, 4/53 (7.5%) of previously irradiated patients died from neutropenic sepsis. There was a further drug-related death from gastro-intestinal haemorrhage in a previously irradiated patient and one patient in this group died from bleomycin lung toxicity.

The data also indicate that the interval of time elapsing between the end of radiotherapy and the start of chemotherapy exerts an important influence on the risk of normal tissue damage. Thus 6/6 patients receiving chemotherapy within 2 months of completing radiotherapy with doses in the range 35-45 Gy developed complications. With intervals of > 2 months the risk of complication was markedly reduced although as shown in Fig. 1 there is a suggestion that even at longer intervals the delivery of chemotherapy modified the response of subcutaneous tissue and bowel to prior irradiation.

The influence of the time interval separating drugs and radiation and the order in which they are delivered has been investigated experimentally although in most cases only short time intervals have been explored. Phillips et al. [8] reported that adriamycin and actinomycin D given 7 days before irradiation of mouse intestine showed no enhanced response whereas drug given 2 hours before or 2 days after resulted in a marked enhancement. More recent data investigating drug-radiation interactions in mouse lung using a non-lethal endpoint have shown that adriamycin, cyclophosphamide and bleomycin have a marked effect on the development of radiation lung damage [2]. With adriamycin, lung damage was greater with simultaneous administration of drug and radiation than when drug was given 28 days after irradiation. However, when drug was given 28 days before irradiation no enhancement was observed. Similarly, simultaneous delivery of cyclophosphamide and radiation produced the greatest modification of lung response although drug given at times 28 days before and after irradiation produced a greater effect than radiation alone. Experimentally derived "time-lines" for drug-radiation interactions on a range of normal tissues have recently been reviewed by Steel [11]. Clinical data on timing and sequencing are more scanty [6]. Interpretation of the clinical data on gastro-intestinal damage is difficult but it is clear that chemotherapy can exacerbate the damaging effect of radiation. For example, Ranson et al. [9] reported that 6/16 children treated with simultaneous drug-radiotherapy for abdominal rhabdomyosarcoma developed severe bowel complications resulting in death in three cases. Clinical data also from experience treating paediatric tumours demonstrates that drugs may enhance late damage in soft tissues [12]. A report from Aristizabal et al. [1] suggests that timing may be important with concurrent radiation and chemotherapy (adriamycin and cyclophosphamide) resulting in cutaneous complications in 4/6 patients whereas 0/14 treated with a drug-radiation sequence separated by a 7–10 day interval developed complications. Limited data in head and neck cancer also demonstrate that the complications observed with simultaneous administration of drugs and radiation may be greatly reduced by the sequential delivery of drugs and radiation [6].

The biological implications of the findings of the present study are twofold. Firstly, the absence of complications in patients given chemotherapy before radiotherapy suggests that, at least for subcutaneous tissue and bowel, recovery from drug-inflicted damage appears to be largely complete by 4–6 weeks. Obviously this hypothesis cannot be extended more generally to include other drugs and other normal tissues, for example, lung tissue exposed to bleomycin or renal tissue to cis-platinum. Secondly, if the chemotherapy employed to treat previously irradiated patients in the present series is conceived as a probe for residual sub-clinical radiation damage there appears to be a process of restitution (to avoid the term "repair" with its more precise connotation) which is certainly incomplete
within the first 2 months, but which appears to lead to recovery, albeit incomplete, in subsequent months. This relatively protracted recovery process might reflect slow repair as described in lung tissue [5] or repopulation of stromal cells, including vascular endothelium, and fibroblasts concerned with collagen biosynthesis. The biological events which are eventually expressed as subcutaneous fibrosis are poorly characterised. Marked fibrosis is uncommon after the delivery of 35–45 Gy to the retroperitoneum using anterior and posterior fields and megavoltage irradiation. Despite this, it is clear that there is a marked perturbation of cells (fibroblasts) concerned with collagen metabolism and that drugs given soon after irradiation may exert a profound effect on presumed cellular recovery leading to the rapid appearance of severe fibrosis in some cases.

References