The effectiveness of hyperbaric oxygen therapy (HBOT) in radiation-induced haemorrhagic cystitis
Vincent Chong, Michael Rice

ABSTRACT

INTRODUCTION: Radiation cystitis is one of the possible complications from pelvic radiotherapy. Hyperbaric oxygen (HBOT) improves tissue oxygenation and healing of scarred tissue.

AIMS: To assess the efficacy of hyperbaric oxygen therapy (HBOT) in the management of radiation-induced haemorrhagic cystitis in patients with urological cancers.

METHODS: This is a retrospective review on all patients with macroscopic haematuria secondary to radiation induced haemorrhagic cystitis who were treated with hyperbaric oxygen therapy (HBOT) between 2009 and 2013. The primary outcome is symptomatic assessment (either complete resolution, partial resolution or no change).

RESULTS: A total of 12 patients with radiation-induced cystitis secondary to urological cancer were included in this study with a mean follow-up of 443 days. The mean age was 78 years. Complete resolution of haematuria was seen in six out of 12 patients. Partial response was achieved in two patients where one required two courses of HBOT and one required three courses of HBOT. As a result, the overall improvement of haematuria after HBOT was 67%. A total of four patients had no response to HBOT.

CONCLUSION: Radiation-induced cystitis is a difficult clinical problem to treat. HBOT is not a magic bullet but it may be another alternative treatment option we have at this point in time.

Radiotherapy is a non-invasive treatment targeting malignant cells and surrounding tissue. Technology advances have resulted in greater treatment efficacy while significantly reducing the level of toxicities. However, radiation cystitis is one of the possible complications from pelvic radiotherapy. It can occur six months to 10 years after irradiation. It has been reported to develop in 6.5% of patients who had radiotherapy for cervical cancer. Radiation therapy causes chronic fibrosis in the poorly oxygenated bladder tissues with eventual tissue scarring. This could lead to bladder mucosal sloughing and hemorrhagic cystitis.

This is a difficult clinical problem to treat. Multiple treatments options have been tried, such as administration of tranexamic acid; blood transfusions; local therapies such as bladder irrigation or instillation of formalin, alum or silver nitrate; invasive procedures such as cysto-diathermy, embolisation and finally cystectomy. Overall results are disappointing.

Hyperbaric oxygen (HBOT) improves tissue oxygenation in previously radiation tissue. This will result in capillary angiogenesis, an increase in fibroblast concentration and healing of scarred tissue.

In this study, we aim to assess the efficacy of HBOT in the management of radiation-induced haemorrhagic cystitis in patients with urological cancers.

Subjects and methods

This is a retrospective review on all patients with radiation cystitis who were treated with hyperbaric oxygen therapy (HBOT) between 2009 and 2013 at Slark Hyperbaric Unit, Devonport and Quay Park Health, Auckland. Ethics approval was gained from the institutional review board.
We included all adult patients presented with macroscopic haematuria secondary to radiation-induced haemorrhagic cystitis. All patients underwent a cystoscopy and imaging of the renal tract to exclude other causes of bleeding. All clinical notes from the hospitals were reviewed.

Data collection
We evaluated patient characteristics (age, gender and ethnicity), primary malignancy site, modality of radiotherapy, onset of haematuria post-radiotherapy, time from haematuria onset to the initiation of HBOT, number of admissions to hospital and prior intravesical management. The onset of haematuria was defined as the first episode of haematuria requiring hospital admission after radiotherapy.

The primary outcome of this study is symptomatic assessment after HBOT (either complete resolution, partial resolution or no change). Complete resolution was defined as absence of macroscopic haematuria. Partial resolution was defined as reduction in the severity or frequency of macroscopic haematuria or requirement for more courses of HBOT.

Oxygen protocol
HBOT was administered in a compression chamber. The overall treatment duration ranged from 90 to 120 min. Treatments scheduled daily for five days a week for 30 to 40 dives (six to eight weeks). Sessions varied in time and duration to ensure patient comfort.

Statistics
Statistical analysis was performed using SPSS 20. Descriptive statistics were expressed as mean, range and standard deviation. Analysis of categorical variables was performed using the chi square test. Statistical significance was reached at a P value of 0.05 or less.

Results
A total of 12 patients with radiation-induced cystitis secondary to urological cancer were included in this study. The mean age was 78 years (range 66 to 85, SD 6.8). All were European male. The primary indications for radiotherapy were prostate cancer in nine patients and bladder cancer in three patients.

The mean time interval between radiation therapy and HBOT was nine years (range 1–18, SD 5.5). The mean time interval between onset of haematuria and HBOT was two years (range 1–5, SD 1.7). The mean number of admissions to hospital for haematuria was four (range 1–6, SD 3.6) prior to HBOT.

Patients were subsequently split into “early” and “late” group where “early” is defined as initiation of treatment within one year of haematuria and “late” as initiation of treatment after one year. There was no significant difference in outcome of haematuria in patients referred early or late with a P value of 0.5 (Table 1).

Prior to HBOT, six patients had other treatments, namely cysto-diathermy, intravesical alum, intravesical prostaglandin and intravesical formalin.

Complete resolution of haematuria was seen in six out of twelve patients. Partial response was achieved in two patients where one required two courses of HBOT and one required three courses of HBOT. As a result, the overall improvement of haematuria after HBOT was 67% (Table 2).

A total of four patients had no response to HBOT. Two patients were on warfarin, one required a cystectomy and ileal conduit due to ongoing haematuria, and another one died during the course of HBOT and was counted as failure due to ongoing haematuria which did not improve.

Mean follow-up period was 443 days (59–1513, SD 474.245). Interestingly, seven patients were known to palliative care on Table 1: Patients referred “early” or “late” for initiation of HBOT.

<table>
<thead>
<tr>
<th></th>
<th>Early (within one year)</th>
<th>Late (after one year)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematuria free</td>
<td>No</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
last follow-up date. The referral mostly came from the Urology service (nine patients) compared to Oncology (two patients) and General Practice (one patient).

**Discussion**

Radiation cystitis is a potentially debilitating side effect for patients. HBOT is the only form of treatment that promotes tissue healing and angiogenesis. Cochrane review concluded that there is some evidence that HBOT improves outcome in late radiation tissue injury affecting bone and soft tissues of the head and neck, for radiation proctitis and osteoradionecrosis. The pathology of radiation injury suggests that other tissues like bladder are likely to respond to HBOT but they did not find enough randomised studies to support this. Our study showed an average short-term efficacy of 67% with HBOT. A review of literature showed that the majority of the studies also reported equivocal responses to HBOT. Among the best rate quoted was an improvement of 100% with 24 months follow-up by Nehemen, 86% with 10 to 120 months follow-up by Cormen, 80% with 12 month follow-up by Chong, 73% with a 39 months follow-up by Oliai, and 76% with a 12 months follow-up by Oscarsson. A systemic review found that 145 (76%) of 190 reported patients demonstrated complete or partial resolution.

On the other hand, long-term outcome is questionable with HBOT. A study from Austria with 10 patients and a follow-up duration up to six years did not yield favourable results, whereas Nakada reported that 87.5% of patients showed an improvement with HBOT with a mean follow-up of 9.8 years.

### Risk factors

The literature commented on several risk factors affecting the outcome of HBOT include age, total radiation dose and duration from onset of haematuria to HBOT. Our mean age was 78 years and that may have contributed to the worse outcome as compared to other studies. We were not able to retrieve all the data on the total radiation dose. We hope that newer methods of radiation delivery should further decrease radiation complications. The timing of HBOT was not a significant factor in our study as opposed to the study by Chong where patients with early HBOT experienced a better response to HBOT with a rate of 96% compared to 66%.

A study from Tasmania on the cost of HBOT revealed that HBOT gave major health cost savings over the study period of 2.5 years but noted that there are significant hidden costs not recorded. After successful HBOT, healthcare costs was saved with no emergency admission or inpatient fees. However, HBOT is not widely accessible and the treatment is given over a relatively long period of six to eight weeks. Patients need to be able to commit to this long period of

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**Table 2:** Symptomatic assessment after HBOT (either complete resolution (Y), partial resolution (Y2) or no change (N).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Cancer diagnosis</th>
<th>Warfarin</th>
<th>RT (year)</th>
<th>HBOT sessions</th>
<th>Haematuria free</th>
<th>No of ED admission (pre)</th>
<th>No of ED admission (post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>Prostate</td>
<td>0</td>
<td>1996</td>
<td>2009</td>
<td>Y</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>Prostate</td>
<td>0</td>
<td>2001</td>
<td>2009, 2010</td>
<td>N</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>Prostate</td>
<td>1</td>
<td>2000</td>
<td>2009, 2010</td>
<td>N</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>Bladder</td>
<td>0</td>
<td>2010</td>
<td>2011, 2012, 2012</td>
<td>Y2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>Prostate</td>
<td>0</td>
<td>1996</td>
<td>2012</td>
<td>Y</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>Prostate</td>
<td>0</td>
<td>2001</td>
<td>2012, 2012</td>
<td>Y2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>Bladder</td>
<td>0</td>
<td>2011</td>
<td>2013</td>
<td>Y</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>Prostate</td>
<td>0</td>
<td>1999</td>
<td>2013</td>
<td>Y</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>85</td>
<td>Prostate</td>
<td>1</td>
<td>1995</td>
<td>2013*</td>
<td>N</td>
<td>6</td>
<td>Deceased</td>
</tr>
<tr>
<td>10</td>
<td>76</td>
<td>Prostate</td>
<td>0</td>
<td>2001</td>
<td>2012, 2013</td>
<td>N</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>Bladder</td>
<td>0</td>
<td>2009</td>
<td>2011</td>
<td>Y</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>84</td>
<td>Prostate</td>
<td>0</td>
<td>2001</td>
<td>2010</td>
<td>Y</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

* Patient 9 died during the course of HBOT and were counted as failure due to ongoing haematuria.
treatment with equivocal success rate. In our study, none of the patients reported any serious complication as an effect of HBOT.

A limitation of our study was the small sample of patients who had radiation cystitis and proceeded to HBOT. This makes it difficult to deduce trends. The literature lacks good randomised trials to evaluate the long-term efficacy of HBOT. Most studies had only short-term follow-up of their patients. More data from larger and longer duration studies is essential to answer the question of efficacy of HBOT. A long-term follow-up with yearly evaluation is currently in progress.

In addition, we were unable to standardise pre-HBOT management. The protocol of HBOT are not standardised between centres and is dependent on severity of problem and patients’ factors. We only recorded haematuria requiring hospital admission. We considered this to be the only meaningful clinical outcome when patients seek medical attention.

In conclusion, radiation induced cystitis is a difficult clinical problem to treat. HBOT offered another treatment option but our study has only shown an overall improvement in 67% of patients. HBOT is not a magic bullet but it may be another alternative treatment option we have at this point in time.

Competing interests:
Nil.

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