PROGNOSTIC SIGNIFICANCE OF RADIATION INDUCED LYMPHOPENIA IN PATIENTS WITH HIGH RISK PROSTATE CANCER

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Summary

Lymphopenia is a known side-effect of radiotherapy but, being usually asymptomatic, its clinical value is just recently being recognized in the light of immunotherapy revival. Here we present clinical and laboratory data of 9 high-risk prostate patients that underwent whole pelvis radiotherapy combined with hormonal therapy. All patients experienced haematological toxicity during their treatment, with lymphopenia being the most profound. In addition, all of them were asymptomatic as regards to observed lymphopenia. After median follow up of 17 months 8/9 patients are still receiving hormonal treatment and have no evidence of their disease. The only patient with relapse discontinued hormonal therapy upon completion of radiotherapy. Therefore, we could not show any detrimental effect of observed lymphopenia on the outcome of these 9 patients.

KEY WORDS: prostate cancer, whole pelvis radiotherapy, radiation induced lymphopenia

INTRODUCTION

Haematological toxicity from post-prostatectomy whole pelvis radiotherapy has been described in literature. Lymphopenia has been observed with standard fractionation (daily fractions of 1.8-2Gy) and neutropenia with hypofractionation (daily fractions >2 Gy) (1). Lymphopenia is defined as a peripheral blood lymphocyte count <1.5x 10⁹/L. Since lymphocytes account for about 20-40% of overall white blood counts, it cannot be
detected without differential blood count. Lymphocytes are the most radiosensitive cells among erythroid, myeloid and lymphoid lineage (2). Lymphocytes staying within or circulating through a radiation portal are affected by radiotherapy; their lethal dose (LD) is 2 Gy and LD90 3 Gy. Other haematological side effects such as thrombocytopenia, neutropenia or anaemia are much more studied compared to lymphopenia given their clinically apparent and acute influence on patients, making them prone to bleeding, infections or fatigue. Effect of radiation on lymphocyte counts has been known for decades (3) but just recently is its potential association with tumour control and patient outcomes being researched, bearing in mind the role of immune system on tumour surveillance.

Aim of this analysis was to address severity and duration of haematological toxicity from whole pelvis radiotherapy in high-risk prostate cancer and its effect on tumour control. Whole pelvis radiotherapy is indicated in patients with high risk prostate cancers undergoing whole pelvis radiotherapy. All 9 patients were irradiated in 2016 and 2017 at University Hospital for Tumours, Zagreb. Patients’ characteristics are shown in Table 1. Median patient age was 77 years (range 66-84), initial PSA values were between 7.15 and >100 ng/mL, 1 patient had prostate adenocarcinoma Gleason score (GS) 3+3, Grade group (GG) 1, 3 patients GS 3+4, GG 2, 2 patients GS 4+3, gg 3, 1 patient GS 3+5, GG 4, 1 patient GS4+4, GG 4, and 1 patient GS 4+5, GG 5. Median follow up (upon completion of radiotherapy) was 17 months (range 9-21 months).

All baseline blood counts values were within normal ranges. Prescribed dose on pelvic lymph nodes was 46 Gy, on seminal vesicles 56 Gy and on prostate 74 Gy, 2 Gy per fraction, 5 days/week. Radiation portals are shown on Figures 1 and 2. In all patients treatment started with whole pelvis irradiation. All patients received androgen deprivation therapy; 3 patients received antiandrogen only (bicalutamide 150 mg) and 6 patients LHRH agonist with antiandrogen (flutamide 3x 250 mg or bicalutamide 50 mg) before and during radio-

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**Table 1**

<table>
<thead>
<tr>
<th>Age</th>
<th>Pre-therapeutic PSA value (ng/mL)</th>
<th>GS</th>
<th>Hormonal therapy</th>
<th>Follow up upon completion of radiotherapy</th>
<th>PSA level/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>77</td>
<td>11.95</td>
<td>4+5</td>
<td>LHRH agonist</td>
<td>21 months</td>
<td>0.01/NED&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>82</td>
<td>53.04</td>
<td>3+5</td>
<td>LHRH agonist</td>
<td>9 months</td>
<td>0.92/NED</td>
</tr>
<tr>
<td>84</td>
<td>29.53</td>
<td>4+3</td>
<td>Bicalutamide 150 mg</td>
<td>12 months</td>
<td>0.05/NED</td>
</tr>
<tr>
<td>66</td>
<td>38.22</td>
<td>4+3</td>
<td>LHRH agonist</td>
<td>9 months</td>
<td>0.01/NED</td>
</tr>
<tr>
<td>77</td>
<td>&gt;100</td>
<td>3+4</td>
<td>Bicalutamide 150 mg</td>
<td>20 months</td>
<td>0.04/NED</td>
</tr>
<tr>
<td>76</td>
<td>52.73</td>
<td>3+4</td>
<td>Bicalutamide 150 mg (for 3 months, before and during RT)</td>
<td>17 months</td>
<td>Biochemical relapse after 14 months (PSA 3.73), bone and lymph node metastases 2 months later (PSA 7.18) /AWD&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>70</td>
<td>53.41</td>
<td>3+3</td>
<td>LHRH agonist</td>
<td>19 months</td>
<td>0.04/NED</td>
</tr>
<tr>
<td>72</td>
<td>31</td>
<td>3+4</td>
<td>LHRH agonist</td>
<td>15 months</td>
<td>&lt; 0.01/NED</td>
</tr>
<tr>
<td>82</td>
<td>7.15</td>
<td>4+4</td>
<td>LHRH agonist</td>
<td>21 month</td>
<td>&lt; 0.002/NED</td>
</tr>
</tbody>
</table>

<sup>a</sup> No evidence of disease

<sup>b</sup> Alive with disease

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**PATIENTS AND METHODS**

We have monitored the counts of absolute white blood cells, lymphocytes, neutrophils, platelets and haemoglobin in 9 patients with high-risk prostate cancers undergoing whole pelvis radiotherapy. All 9 patients were irradiated in 2016 and 2017 at University Hospital for Tumours, Zagreb. Patients’ characteristics are shown in Table 1. Median patient age was 77 years (range 66-84), initial PSA values were between 7.15 and >100 ng/mL, 1 patient had prostate adenocarcinoma Gleason score (GS) 3+3, Grade group (GG) 1, 3 patients GS 3+4, GG 2, 2 patients GS 4+3, gg 3, 1 patient GS 3+5, GG 4, 1 patient GS4+4, GG 4, and 1 patient GS 4+5, GG 5. Median follow up (upon completion of radiotherapy) was 17 months (range 9-21 months). All baseline blood counts values were within normal ranges. Prescribed dose on pelvic lymph nodes was 46 Gy, on seminal vesicles 56 Gy and on prostate 74 Gy, 2 Gy per fraction, 5 days/week. Radiation portals are shown on Figures 1 and 2. In all patients treatment started with whole pelvis irradiation. All patients received androgen deprivation therapy; 3 patients received antiandrogen only (bicalutamide 150 mg) and 6 patients LHRH agonist with antiandrogen (flutamide 3x 250 mg or bicalutamide 50 mg) before and during radio-
therapy. Complete blood sample was obtained before the beginning of radiotherapy and then weekly during the treatment.

RESULTS

In all patients persistent decline of absolute white blood cells count (WBC) and haemoglobin level (Hb) was observed (WBC till 3.28x 10^9/L, Hb till 104 g/L) (Charts 1 and 2). No change in neutrophil and platelet counts was noticed. A significant decline of lymphocyte count was observed in all patients, both in absolute values and percentage, with nadir values between 0.39 and 0.79x 10^9/L (median 0.54x 10^9/L) (Chart 3). Lymphopenias occurred from 5th week of radiotherapy onwards, with doses ranging from 44 to 66 Gy (median being 52 Gy), hence 30 till 45 days from the beginning of whole pelvis radiotherapy (median 36th day). By the end of radiotherapy lymphocyte counts gradually increased, but without reaching referral values (1.19- 3.35x 10^9/L). All observed lymphopenias were asymptomatic, both during and upon completion of radiation treatment.

After a median follow up of 17 months, 8 patients are without evidence of their disease and all of them are still receiving hormonal treatment: two patient bicalutamide and 6 patients LHRH
agonist. One patient had biochemical relapse after 14 months and 2 months later positron emission tomography (PET) scan revealed bone and lymph node metastases. That patient discontinued hormonal treatment with bicalutamide after completion of radiotherapy.

**DISCUSSION**

Although well-known for decades, effect of radiation on lymphocyte counts has recently become more and more interesting, following immunotherapy revival. Lower number of circulat-
ing lymphocytes could be associated to lower tumour lymphocyte infiltration and weaker immunological anti-tumour response, all of which could translate into worse outcome.

According to literature data, association of treatment induced lymphopenias and worse outcome was observed in patients with glioblastoma, head and neck squamous cancer, nasopharyngeal cancer, both non-small and small cell lung cancer, pancreatic cancer, oesophageal cancer and breast cancer (2).

As far as pelvic malignancies are concerned, two trials found association between lymphopenia and worse outcome, both in patients with cervical cancer undergoing chemoradiotherapy. Wu et al. found threshold lymphocyte value of $<0.5 \text{cells/mm}^3$ 2 months upon completion of the treatment being associated with worse median overall survival: 21.2 vs 45.0 months, $P = 0.03$ (5). Cho and al. analysed 124 patients with FIGO stage I-III cervical cancer who received weekly cisplatin-based concomitant chemoradiotherapy and brachytherapy. Patients with lymphopenia gr 2-3 had 5-year disease specific survival (DSS) and 3-year progression specific survival (PFS) significantly higher compared to those with grade 4 lymphopenia (defined as $<200 \text{cells/l}$): 84.8\% vs. 50.4\%, $p<0.001$, and 80.7\% vs. 50\%, $p=0.002$, respectively (6).

Our patients did not receive concurrent chemotherapy, which is known to also have an effect on lymphocyte counts. Since all of them experienced lymphopenia, we could not make any clear conclusion on its effect on their outcome. The only patient that had disease recurrence discontinued hormonal treatment upon completion of radiotherapy. Overall his hormonal therapy lasted for 3 months, which is in contrast with recommended duration of two to three years for this subset of patients.

**CONCLUSION**

Clinically unapparent lymphopenia occurred in all 9 patients during radiotherapy, starting from 30 to 45 days from the beginning of the treatment. After median follow up of 17 months 8/9 patients are without evidence of the disease. Although patient sample is quite small and follow up is short, it can still be concluded that lymphopenia did not have any effect on tumour control. One relapse should rather be attributed to hormonal therapy discontinuation than to changes in immunological anti-tumour effect caused by radiation induced lymphopenia.

**LITERATURE:**


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