Chromosomal analysis of peripheral lymphocytes of patients before and after radiation synovectomy with samarium-153 particulate hydroxyapatite

E. K. O’Duffy, F. J. Oliver¹, S. J. Chatters¹, H. Walker¹, D. C. Lloyd², J. C. W. Edwards³ and P. J. Ell

Institute of Nuclear Medicine, University College London, ¹Department of Haematology, University College Hospital, ²National Radiological Protection Board, Chilton, Oxon and ³Department of Rheumatology, University College London, London, UK

Abstract

Objective. Radiation synovectomy may be indicated for the treatment of chronic synovitis. A number of factors may affect its current use, including availability, limited evidence for its efficacy compared to intra-articular glucocorticoid, and concerns regarding the potential long-term effects of radiation exposure, particularly in younger patients. Specific chromosome-type abnormalities in peripheral lymphocytes can be useful indicators of whole-body radiation exposure. The frequency of these aberrations has been shown to increase in patients who have had radiation synovectomy using yttrium-90 by up to five times compared to baseline levels. Samarium-153 particulate hydroxyapatite (Sm-153 PHYP) is a new radiopharmaceutical currently on trial which appears to have less extra-articular leakage than yttrium-90 compounds. The aim of this study was to identify any increase in specific chromosome-type abnormalities, using published criteria, in patients following Sm-153 PHYP synovectomy of the knee. The 10 patients (five men, five women) in whom the analyses were performed had a mean age of 47 yr (range 28–70 yr).

Results. There was no increase in scored chromosome-type abnormalities after Sm-153 PHYP synovectomy.

Conclusion. This study further supports the relative safety of Sm-153 PHYP compared to other radiopharmaceuticals.

Key words: Chromosome, Radiation synovectomy.

Treatments involving different forms of radiation continue to be used in a number of non-malignant conditions, including skin disease, inflammatory arthritis and hyperthyroidism. The majority of therapeutic options have potential adverse effects; risk–benefit ratios must always be considered. A number of studies have assessed the effects of low-dose radiation and reassuring results have encouraged its ongoing use [1]. The evidence for the safety of radioactive iodine-131 in the treatment of hyperthyroidism has encouraged its widespread use in patients over 18 yr old [2]. There is no clear evidence for an increase in malignancy following radiation synovectomy, although there have been a few individual case reports [3–5].

The assumption of the linear non-threshold hypothesis (ICRP) for radiation-induced malignant disease means that any exposure, however low, must carry some risk. This is generally accepted as a prudent stance, even though empirical evidence of increased cancer rates from epidemiological studies of low-dosed populations has proved elusive [6]. In the context of synovectomy, the development of new radiopharmaceuticals has been aimed at refining the characteristics of the compound to maximize the dose maintained within the joint and thus reduce unwanted exposure of extra-articular tissues. Studies assessing an increased risk of malignancy require large numbers and long-term follow-up, e.g. the lifespan study of Japanese A-bomb survivors [7]. Information from other methods is often used and chromosomal analysis is a technique that can rapidly identify cytological damage following quite low levels of irradiation. Exposure to environmental carcinogens is associated with an increase in chromosomal aberra-
tions in peripheral lymphocytes. These cytogenetic end points are also markers for increased cancer risk [8].

Several factors affect the potential risk of radiation, including the type and total dose of radiation. Extrapolating information from other circumstances of whole-body radiation exposure, the most important sites for potential neoplastic change are the lymph nodes and washes in methanol:acetic acid (3:1). The prepared slides from the joint [9, 10]. The high proportion of unwanted in vivo remain tightly bound have a relatively short half-life, be primarily a

as the presence of 46 centromeres by staff of the University College Hospital London cytogenetics unit. The criteria for scoring chromosome-type abnormalities were followed as previously described [20]. Other chromatid-type aberrations were also recorded. The number of cells scored varied from patient to patient (Table 1), but for any one patient the same number was scored for the pre- and post-treatment specimens.

Results

Clinical details (Table 1)
The 10 patients (five men, five women) in whom the analyses were performed had a mean age of 47 yr (range 28–70 yr). Four of the patients were known to have rheumatoid arthritis; four had undifferentiated seronegative oligoarthritis and two had psoriatic arthritis. The median disease duration was 7 yr (range 2–25 yr).

Chromosome-type aberrations (Fig. 1)
The number of chromosome-type abnormalities observed was small, with no significant difference in the number of abnormalities before and after treatment. In this sample of 6160 cells, a background level of ~3–6 dicentrics would be expected. Analysis showed four dicentrics, 20 acentric fragments and no acentric rings or minutes.

Chromatid-type aberrations
Chromatid breaks and exchanges were also scored. There was no clear correlation between these abnormalities and exposure to disease-modifying drugs.

Quality analysis
Coded slides from two patients were analysed by independent scorers at the National Radiological Protection Board. There was good correlation between chromosome-type aberration scores from the two groups of observers.

Discussion
There are currently two main methods of assessing chromosomal damage: aberration analysis, as performed in this study, and the identification of micronuclei. Micronucleus detection has advantages: scoring is quick and inter-observer variability is minimal. The main
Table 1. Summary of results showing chromosome analyses and clinical histories

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>No. cells scored</th>
<th>Dicentrics Pre</th>
<th>Dicentrics Post</th>
<th>Chromatid breaks and exchanges Pre</th>
<th>Chromatid breaks and exchanges Post</th>
<th>Injected activity (MBq)</th>
<th>Cigarette smoking (cigs/day)</th>
<th>Current DMARDs</th>
<th>Previous DMARDs</th>
<th>Diagnosisb</th>
<th>Disease duration (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>500</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>6</td>
<td>718</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>33</td>
<td>80</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>7e</td>
<td>618</td>
<td>6</td>
<td>25</td>
<td>–</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>40</td>
<td>500</td>
<td>1</td>
<td>1</td>
<td>14</td>
<td>12</td>
<td>840</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>57</td>
<td>300</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>6</td>
<td>567</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>37</td>
<td>300</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>6</td>
<td>630</td>
<td>3</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>47</td>
<td>150</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>2</td>
<td>720</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>1,2,4,5</td>
</tr>
<tr>
<td>54</td>
<td>500</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>3</td>
<td>634</td>
<td>1</td>
<td>25</td>
<td>3</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>42</td>
<td>150</td>
<td>2</td>
<td>–</td>
<td>5</td>
<td>1</td>
<td>563</td>
<td>15</td>
<td>15</td>
<td>4</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>62</td>
<td>300</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>3</td>
<td>412</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>1,4,6</td>
<td>2</td>
</tr>
<tr>
<td>55</td>
<td>300</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>11</td>
<td>696</td>
<td>30</td>
<td>25</td>
<td>4</td>
<td>–</td>
<td>2</td>
</tr>
</tbody>
</table>

aDMARDs (disease-modifying drugs). 1 = Myocrisin, 2 = penicillamine, 3 = methotrexate, 4 = sulphasalazine, 5 = azathioprine, 6 = hydroxychloroquine, 7 = cyclosporine.
bDiagnosis. 1 = Rheumatoid arthritis, 2 = psoriatic arthritis, 3 = undifferentiated seronegative arthritis.
c3 in one cell.
Overall, the yields per cell of chromatid aberrations amongst the 10 patients vary by about an order of magnitude. This may well reflect their different anti-inflammatory and analgesic drug histories, although the data are too few to conclude or implicate any particular drug combination.

Conclusion

These results offer further evidence for the relative safety of Sm-153 PHYP as a radiopharmaceutical in the treatment of chronic synovitis. Previously published data on extra-articular leakage also support its favourable characteristics when compared with Y-90.

References