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ORIGINAL ARTICLE *Musculoskeletal*

Radioactive synovectomy with ^{90}yttrium and ^{153}samarium hydroxyapatite in haemophilic joints: preliminary study on radiation safety

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Summary. Most countries still do not achieve 1 IU of factor VIII/capita sufficient for survival. Although primary prophylaxis prevents synovitis, is not universally used. Chronic synovitis is treated with arthroscopy at expense of considerable amount of coagulation factors, and specialized surgeons. Radioactive synovectomy (RS) is a minimally invasive and cost effective alternative to arthroscopy, often considered first the option for persistent synovitis. Even without established causation with cancer, RS is avoided by some, due to this concern. We aim contributing to the understanding of RS safety regarding malignancy, presenting a large number of treated patients, and a single case of cancer. Three centres in Brazil applied RS with ^{90}Yttrium Citrate, ^{90}Yttrium hydroxyapatite or ^{153}Samarium hydroxyapatite in haemophilic joints and performed a survey addressing cancer in these patients. Four hundred and eighty eight patients (ages 3–51) received 1–3 RS (total 842) and follow-up was 6 months to 9 years. One patient aged 14 years presented Ewing sarcoma, 11 months after RS. The tumour was treated successfully with surgery and chemotherapy. Causality of cancer by RS is improbable in this case. Accordingly, latency here is far below minimum 5–10 years for radio-induction of solid tumours. Moreover, ES is not a typically radio-induced tumour, even at high doses. In agreement with others, though recognizing limitations, this study suggests RS is safe regarding cancer induction. Synovitis is a known burden for patients. The decision of making reasonable usage of RS should be outweighed with the risks of leaving synovitis untreated.

Keywords: cancer, haemophilia, radiosynovectomy, samarium, synovitis, yttrium

Introduction

Chronic haemophilic synovitis and arthropathy, the main complications of haemophilia, can affect one or more joints [1]. The gold standard of prophylactic treatment and comprehensive care are not available in many countries. Nearly two thirds of the world does not achieve the minimum target of 1 IU of clotting factors concentrates (CFC) per capita, only sufficient for survival [2,3]. Moreover, some patients under secondary or primary prophylaxis, as well as those with inhibitors, may require locally directed treatment of synovitis [4–7]. Synovitis can be treated with arthroscopic surgery at the expense of considerable amount of CFC, and by specialized orthopaedic surgeons [4,5,7]. These are conditions beyond reach of many patients and countries.

Radioactive synovectomy (RS), intra-articular injection of radiopharmaceuticals, is a minimally invasive and highly cost effective alternative to arthroscopy, being for some authors, the first option when prophylaxis fails to control synovitis. [4,5,7]. RS is used since 1962 in developed and developing countries with no proven causal association with cancer, according to the studies published so far [4–21]. However, ionizing

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radiation carries intrinsic concerns on malignancy development, which refrain some clinicians from using this therapy [16,19–21].

In this article, we aim to contribute to the understanding of RS safety regarding cancer. This is an important topic, in which the collaboration from multiple centres is considered essential. Here, we show preliminary data that possibly support the hypothesis that the benefits of RS outweigh its risks in the treatment of synovitis, a key issue for haemophilia.

Patients and methods

Radioactive synovectomy

From April 2003 to November 2011, 488 patients with haemophilic synovitis, upon referral of their haematologists, were submitted to 842 RS at one of the following centres: Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro (HUCFF), Hemocentro de Mato Grosso (Hemomat) and Hospital de Clinicas da Universidade Federal do Paraná (HC-UFPR). The three centres used the same RS protocol, detailed in other articles [13,14], but the type of radiopharmaceutical, either ^{90}Yttrium Citrate (^{90}Y-C), ^{90}Ytrium Hydroxyapatite (^{90}Y-HA) or ^{153}Samarium Hydroxyapatite (^{153}Sm-HA) varied according to their availability at the time of RS (Table 1). We used the following activities of ^{90}Y-C and ^{90}Y-HA: 5 mCi (185 mBq) for knees, 3 mCi (111 MBq) for elbows and ankles and 4 mCi (148 MBq) for shoulders. For ^{153}S-HA we used 10 mCi. Hemomat and HC-UFPR used ^{90}Y-C (CIS-Bio International, Centre D'Etudes Nucleaires de Marcoule, Bagnols/Ceze, France) or ^{90}Y-HA (Instituto de Pesquisas Energéticas e Nucleares – IPEN, Sao Paulo, Brazil) in all joints until 2008, again depending on local availability of these compounds. As from 2008, Yttrium compounds were replaced by ^{153}S-HA for RS in elbows and ankles performed at Hemomat and HUCFF. Each joint was treated up to three times, with a 6-month interval and if indicated, multiple joints from the same patient were treated to a maximum of 400 MBq per patient per day. First, we infiltrated the region with lidocaine 2%, followed by the radiopharmaceutical injection and lastly, triancinolone hexacetonide. The limb was immobilized for the next 48 h and partial weight bearing with crutches was allowed after the 3rd day of RS. Radioactive extra-articular leakage was checked through whole body and local scintigraphy. All centres approved the study through local institutional ethics committees, including written informed consent by all patients.

Cancer survey

We sent a questionnaire by e-mail to the 28 haematologists who had referred patients to one of our centres. The questions were as follows: (i) Have any of your patients submitted to Radioactive Synovectomy (a list of patients is included) died? (ii) Have any of your

Table 1. Centre description of patients submitted to radioactive synovectomy.

	Hemomat	%	HU/UFPR	%	HUCFF/UFRJ	%
Gender						
Male	244		139		100	
Female	3		2		0	
Age (median/years)	13 (3–45)		14 (4–51)		14 (5–34)	
SD	7.5		7.5		6.3	
Diagnosis						
HA	220	89.1	126	89.4	85	85
HB	20	8.1	12	8.5	15	15
vWD	7	2.8	3	2.1	0	0
Inhibitor to FVIII or IX	29	11.7	6	4.3	9	9
Joints						
Knees	219	46.1	79	35.3	73	51
Elbows	135	28.4	84	37.5	37	25.9
Ankles	113	23.8	54	24.1	33	23.1
Shoulders	8	1.7	7	3.1	0	0
Total number of joints	475		224		143	
Radiopharmaceutical						
C Y-90	278	58.5	224	100	0	0
HA Y-90	97	20.4	0	0	54	37.8
HA Sm-153	100	21.1	0	0	89	62.2

Hemomat: Hemocentro de Mato Grosso, Cuiaba, Brazil; HU/UFPR: Hospital de Clinicas da Universidade Federal do Paraná, Curitiba, Parana, Brazil; HUCFF/UFRJ: Hospital Universitario Clementino Fraga Filho/Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil; HA: haemophilia A; HB: haemophilia B; VWD: von Willebrand's disease; C Y-90: Yttrium90 Citrate; HA Y-90: Yttrium90 Hydroxyapatite; HA Sm-153: Samarium153 Hydroxyapatite. SD: Standard deviation.

patients submitted to Radioactive Synovectomy presented oncologic disease? (iii) If the answer to the previous questions is 'yes', what was the cause of death? or What was the diagnosis and localization of the tumour? Codes between C00 and C97 from the International Classification of Diseases version 10 (ICD-10) were considered as oncologic diseases.

Results

Radioactive synovectomy

The results of the RS with ^{90}Y-C and with ^{90}Y-HA achieved by Hemomat are detailed on previous reports [13,14] and the outcomes analysed were the annual frequency of haemarthrosis, articular pain and joint range of motion. Briefly, in 245 joints from 190 patients submitted to RS with ^{90}Y-C, the mean number of bleeds per year was reduced from 19.8 to 2.6. It was also noted reduction of pain and improvement of ROM in most joints [13]. Similar results were achieved with ^{90}Y-HA [14]. The results of RS with ^{153}S-HA and ^{90}Y-HA done at HUCFF are underway to analysis for future reports. Likewise, the results of RS performed at HC-UFPR are subject of yet unpublished reports. Thus, this study is particularly focused on the results of the cancer survey described below.

Results of cancer survey

From the 842 RS (Table 1), 31 joints (20 patients) were treated twice and three joints (three patients) were treated three times. Age ranges, median and standard deviation are detailed on Table 1. The length of follow-up on these patients ranged from: 6 to 16 months at HUCFF, 2–5 years at HC-UFPR and 3–9 years at Hemomat. Four of the 488 patients treated died from circumstances not related to RS: acute pulmonary oedema, liver cirrhosis due to coinfection by hepatitis B and C viruses; homicide and intracranial bleeding after head trauma. One patient, 14 years old when submitted to RS, developed Ewing sarcoma (ES) in the soft tissue of his right scapula. The disease was noticed 11 months after single and uneventful injections of ^{90}Y-HA in knees and one injection of ^{153}Sm-HA in right elbow. He did not present extra-articular leakage of the radioactive products after RS. He had a radiological Pettersson score of 7, 8 and 6 on the right knee, left knee and right elbow respectively. This patient presented a reduction in the number of bleeds in the treated joints from seven (right knee), 24 (left knee) and 24 (right elbow) 6 months before treatment to one (right knee), five (left knee) and two (right elbow) bleeds after 6 months of RS. He had a satisfactory response to surgery and chemotherapy for the ES. This was the only case of cancer after RS in this set of patients.

Discussion

Brazil provides CFC to 100% of 10,065 people with haemophilia (16,194 people with bleeding disorders) within public health system [2]. Nevertheless, this only totals 1.15 IU/capita of factor VIII distributed by the 151 Hemophilia Treatment Centres (HTCs) [2]. Recently, Brazilian government approved a programme for primary prophylaxis, but most children and adults do not meet the selection criteria, due to age older than three or because of already installed target joint. Thereby, RS still presents an important therapy for this large population.

Brazilian Ministry of Health maintains a registry of inherited bleeding disorders (Web *Coagulopatias),* for surveillance of epidemiologic data brought by the HTCs [22]. The haematologists locally responsible for this database are the same who referred the patients to our study. As they must record and update several clinical and laboratorial information from all patients registered at their HTC, infrequent and serious events such as cancer and death, if occurred to one of their patients, would probably be recalled. To help the doctors recalling, a short list with patients name (about 13/centre) was provided with the questionnaire. Considering these are severe or moderate patients (typically symptomatic) we presume they attended several times per year because they cannot obtain CFC out of the HTCs.

Web Coagulopatias currently does not have detailed records of types of cancer. Likewise the National Cancer Registry does not include haemophilia status [23]. Thus, we could not compare cancer incidence between groups of exposed and unexposed subjects, and general population.

Presently, the radionuclides most used for RS in haemophilia are Yttrium (^{90}Y), Rhenium (^{186}Re), Dysprosium (^{165}Dy), Phosphorus (^{32}P) and Samarium (^{153}Sm), and they generally achieve good results [4–15,19]. The usage of radiopharmaceutical varies according to national regulatory guidelines, availability and cost, as well as to the level of tissue penetration and thickness of synovia [5,15]. The materials currently produced and accepted in Europe are ^{90}Y-Citrate or Silicate for knees, ^{186}Re-sulphide colloid for mid-sized joints and ^{169}Er-colloid for small joints, but ^{32}P is not approved. In contrast, the radionuclides produced and approved for RS in the United States are ^{32}P and ^{165}Dy, but not ^{90}Y [4–9]. Other new radiopharmaceuticals have been used for RS. Noteworthy are ^{166}Holmium-Hydroxyapatite, ^{188}Re microspheres and ^{153}Sm-Hydroxyapatite, large-sized particles, a possible advantage because of the low risk of leakage from the joint and consequent irradiation of extra-articular tissues [24]. The latter is produced in Brazil at a low cost, and showed encouraging results in mid-sized joints, an effect attributable to its lower level of penetration [12].

Brazilian centres use since 2003, ^{90}Y Citrate [13], ^{90}Y Hydroxyapatite [14] and ^{153}Sm-Hydroxyapatite [12]. Our selection was mostly based on the local availability of products and Brazilian regulation on nuclear energy. Moreover, because of insufficient comparative studies between different radiopharmaceuticals, we relied on the reports of success achieved with several products, by previous authors. Hence, Kavakli *et al.* in 2006 reported good results with ^{90}Y for all joints [11] and Rodriguez-Merchan *et al.* used ^{90}Y for knees and other joints as far as 2003, achieving especially good results in the elbows [25]. The latter group analysed the characteristics that influenced response to RS, and among other conclusions they found that improvement seemed independent of the isotope used [25,26].

Regarding the potential radiation induction of RS, some studies detected chromosomal abnormalities and somatic cell mutations which arose after RS, but these changes were rare and disappeared over time [6–9, 17–21]. Furthermore, there are a few reports of malignancy associated with RS, most after using Gold (^{198}Au) in rheumatoid arthritis (RA), one case after ^{90}Y in RA [6–9] and two cases of leukaemia after RS with ^{32}P in children with haemophilia, none with established causality [6,7]. Vuorela *et al.* analysed RS with ^{90}Y-Silicate in 143 patients with RA and found nine cases of cancer. As the expected incidence among the general population was 14.9, they concluded that the treatment was safe in the long term (30 years of follow-up) [18]. Perez *et al.* reported RS with ^{32}P in patients with haemophilia (71.6%) or RA (9.5%) followed up for 8.5 years and found no documented cases of malignancy [16]. Recently Infante-Rivard *et al.* published a study of cancer incidence in patients submitted to RS on a 25-year period [21]. They analysed 4860 RS in adults receiving 1–16 knee injections of ^{90}Y, ^{32}P, ^{198}Au, ^{153}Sm or ^{169}Er. Most patients (88%) had RA or other inflammatory synovitis. The incidence of cancer was compared within exposed and unexposed RA patients as well as to the reference population. Although 151 malignant tumours were identified during the study period, incidence of cancer was not considered higher than expected [21].

Despite several models developed to quantify risks of radiation-associated cancers, they are mostly applied to high radiation doses [27]. Studies addressing low radiation doses (such as the ones used on RS) are challenging, as the probability of cancer is similar between exposed and general population [27,28]. Furthermore, haemophilia is rare and most studies only manage to gather few subjects within some categories, tending to limit generalization of the results.

The peak incidence of ES occurs in adolescence and the patient in this study was on adolescence, when treated. Most studies addressing ES and radiation report an increased risk of secondary cancers following radiotherapy for ES, but not the risk of ES following radiation exposure [29]. It is not possible to rule out a radiation effect in this case, considering the theoretical risk present in any amount of radiation. However, this type of cancer is not known to be induced by ionizing radiation, even at high doses [29]. Moreover, the latency time between the RS and the onset of the tumour (11 months) is far below the expected time (5–10 years) for a radiation-induced solid cancer [28]. Considering the facts involved in this case, it is improbable that there is a causal relationship between the onset of the malignancy and the RS.

Compared with other groups [18,21], our set of patients is more homogeneous, regarding underlying diagnosis and gender. Accordingly, although one study had only patients with RA [18] and other had 59 (2.5%) subjects with haemorrhagic disorders and 37% males [21], we present a group of 488 subjects, 99% males, mostly children and adolescents (median 13–14 years) and 100% with haemophilic synovitis. Although we have a short follow-up period (6 months –9 years) when compared with the above-mentioned studies, this is an ongoing study in conjunction with several centres in Brazil, hence the patients will continue to be tracked.

In conclusion, this report suggests that RS was safe regarding cancer induction in this group of patients, which will be continuously tracked. Nevertheless, the limitations of the study might not permit generalization of the results. Currently, the existing reports do not show an increased risk of cancer after RS with several radiopharmaceuticals. However, long-term surveillance at multiple centres is essential to the understanding of RS safety. Chronic haemophilic synovitis is a known burden for patients and families. The benefits of reasonable use of RS seem to outweigh the risks of leaving synovitis untreated.

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