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Increased risk of myeloid leukaemia in patients with ankylosing spondylitis following treatment with radium-224

R. R. Wick[1], E. A. Nekolla[2], M. Gaubitz[3] and T. L. Schulte[4]

Objective. To investigate long-term health effects in AS patients treated with ^{224}Ra.
Methods. A prospective epidemiological study has been carried out on 1471 AS patients treated with repeated intravenous injections of ^{224}Ra between 1948 and 1975. These patients have been followed together with a control group of 1324 AS patients not treated with radioactive drugs and/or X-rays. Numbers of malignancies expected in a normal population were computed from German and Danish cancer registry data.
Results. After a mean follow-up time of 26 yrs in the exposed group or 25 yrs in the control group, causes of death have been ascertained for 1006 exposed patients and 1072 controls. In particular, 19 cases of leukaemia were observed in the exposure group (*vs* 6.8 cases expected, $P < 0.001$) compared to 12 cases of leukaemia in the control group (*vs* 7.5 cases expected). Further subclassification of the leukaemia cases demonstrated a high increase of myeloid leukaemia in the exposure group (11 cases observed *vs* 2.9 cases expected, $P < 0.001$), especially a high excess of acute myeloid leukaemias (7 cases observed *vs* 1.8 cases expected, $P = 0.003$), whereas in the controls the observed cases are within the expected range (4 myeloid leukaemias *vs* 3.1 cases expected).
Conclusions. The enhanced leukaemia incidence in the exposed group is in line with results from experiments in mice injected with varying amounts of the bone-seeking α-emitter ^{224}Ra. In these studies, in animals exposed to lower doses of ^{224}Ra, i.e. at doses lower than those found to induce osteosarcomas, an increased risk of leukaemia was observed.

Key words: Ankylosing spondylitis, Radium-224, Radiopharmaceutical, Late effects, Radiation risk, Malignant disease, Myeloid leukaemia, Follow-up study, Humans, Adult.

Introduction

AS is one of the most common systemic inflammatory rheumatic diseases with a prevalence of 0.1–0.9%, with men being more affected than women (ratio 2:1) [1, 2]. Patients tend to start to consult a physician at about 26 yrs of age [3]. As patients are usually young, AS is of major socioeconomic interest [4]. The first clinical sign is usually inflammatory back pain due to a sacroiliitis that may extend to the spine as spondylitis, spondylarthritis and spondylodiscitis; progressive ankylosis due to syndesmophytes may follow as well as peripheral arthritis, enthesitis and uveitis [5]. The course of the disease is either chronic or intermittent with intervals, of varying lengths, free of complaints. There is a high correlation between the prevalence of the human leucocyte antigen HLA-B27 and the incidence and prevalence of AS [6]. AS should be treated individually with regard to current manifestations of the disease (axial, peripheral entheseal, extra-articular), the level of present symptoms, clinical findings and prognostic indicators (disease activity, inflammation, pain, function, disability, handicap, structural damage, hip involvement, spinal deformities), the general clinical status (age, sex, co-morbidity, concomitant drugs) as well as expectations of the patient [5]. Nowadays an optimal management requires a combination of non-pharmacological and pharmacological treatments, sometimes surgery [5]. Radiotherapy with X-rays is no longer part of internationally accepted treatment recommendations.

In the 1940s treatment with radium-224 (^{224}Ra) was introduced in Germany for the treatment of various diseases [7, 8]. Patients, many of them children or juveniles were injected intravenously with higher doses of ^{224}Ra, up to a cumulative activity of 140 MBq. However, a striking increase of malignant bone tumours was found in a group of patients, particularly in those who received this treatment before the age of 21. These patients were followed in an earlier study of patients with higher doses by Spiess and co-workers [9–14].

Good clinical results were reported for AS patients, describing a long-lasting benefit with a reduction in the need of antirheumatic and analgesic drugs. The method of treating AS with lower doses of ^{224}Ra, first used on a large scale at the Orthopaedic University Hospital at Münster [15], was afterwards adopted by other institutions [7, 16–18], until this treatment with ^{224}Ra was abandoned in 1990. Between 2000 and 2005, ^{224}Ra was re-approved for the treatment of AS patients in Germany, using the previous protocol with lower activities [19].

Few recent studies are available examining immediate side effects and being important for risk considerations in AS patients treated with ^{224}Ra [20–23]. Stephan *et al.* [22] found chromosomal aberrations in peripheral lymphocytes immediately following ^{224}Ra treatment. Lassmann *et al.* [23] introduced new dosimetric calculations for dose estimates for many soft tissues and organs.

Since 1971 an epidemiological study has been carried out at the GSF—National Research Center for Environment and Health, together with 10 orthopaedic and rheumatic hospitals on the late somatic radiation risk to AS patients from treatment with ^{224}Ra [15–17, 24–27]. These investigations should complement results from the above-mentioned study by Spiess and co-workers and examine the risk of the ^{224}Ra treatment of AS.

Although current treatment concepts for AS no longer include radiotherapy using ^{224}Ra, long-term investigations of late effects in a controlled study are of major clinical relevance.

Study population

The original study group included 1588 AS patients treated in the years 1948–75 with repeated intravenous injections of ^{224}Ra. The majority of the patients received one series of 10 weekly injections

[1]GSF—National Research Center for Environment and Health, Institute of Radiobiology, [2]Federal Office for Radiation Protection, Department of Radiation Protection and Health, Neuherberg, [3]Department of Rheumatology and [4]Department of Orthopaedics, University Hospital Münster, Münster, Germany.

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Correspondence to: R. R. Wick, GSF—National Research Center for Environment and Health, Institute of Radiobiology, Ingolstädter Landstr. 1, PO Box 1129, D-85758 Neuherberg. E-mail: wick@gsf.de

Table 1. Follow-up status and exposure parameters of the AS patient study group

	Exposure group	Control group
Total number of patients	1588	1456
Additional treatment with X-rays	109	128
Deleted for other reasons	8	4
Remaining patients	1471	1324
Deceased patients, cause of death certified	1006	1072
Mean injected amount of ^{224}Ra (MBq/kg)	0.17	–
Mean α-dose to the skeleton (Gy)	0.67	–
Mean injection period (weeks)	10.4	–
Mean follow-up time (yrs)	26.3	24.6

Table 2. Observed and expected numbers of leukaemias (ICD-9)

	Exposure group			Control group		
	Observed	Expected	*P*-value	Observed	Expected	*P*-value
Leukaemia (ICD 204–208)	19	6.8	<0.001	12	7.5	0.08
Myeloid leukaemia (ICD 205)	11[a]	2.9	<0.001	4	3.1	–
CML (ICD 205.1)	3	1.0	0.08	1	1.1	–
AML (ICD 205.0)	7	1.8	0.003	3	2.0	–
Lymphatic leukaemia (ICD 204)	7	2.7	0.02	6	3.0	0.08

[a]Including one case of myeloid leukaemia not specified as acute or chronic.

of about 1 MBq each. This is in accordance with the usual dosage of the more recent treatment, resulting in a cumulative dose of 0.56 Gy to the marrow-free skeleton of a 70 kg reference man. There were, however, also patients, who received more than 10 injections per series, resulting in a higher mean for the total study group (Table 1).

A control group of AS patients has been established to provide comparative information on causes of death and on health problems potentially related to the basic disease itself or to its treatment with drugs. In order to avoid a preselection bias with regard to severity of the disease, accompanying diseases or other variables that might be seen as a contraindication for ^{224}Ra treatment, the control group has been drawn mainly from patients out of a hospital known to refuse the ^{224}Ra treatment on principle; only a minority of the controls were from hospitals using ^{224}Ra therapy.

Due to a male predisposition and the diagnostic methods known at the time of recruiting AS patients, most of the patients in this study are male (90.5% in the exposure group, 91.8% of the controls). After the establishment of the association of HLA-B27 with AS in 1973 [28], the male:female ratio changed from an initial 10:1 to 2:1 in favour of males. The reason for this discrepancy is an underdiagnosis of the disease in females before HLA-B27 typing and a tendency of a higher degree of severity of the disease in males [29].

Information on current status is obtained from questionnaires sent periodically to the patients. Causes of death were ascertained from hospital records, from death certificates or from reports of family doctors. They were classified according to the International Classification of Diseases (ICD, 9th revision).

Results

The observed and expected numbers of different types of leukaemia in the exposed and control group are given in Table 2. The expected numbers for a 'normal' population have been calculated on the basis of age-, sex- and calendar-year-specific incidence rates for these tumours from cancer registries. As no national cancer registry exists for Germany, data from the cancer registry of the German state Saarland and of Denmark were used.

Particularly striking are the elevated rates of leukaemia in the exposed group. Up to now, 19 cases of leukaemia were observed compared to 6.8 expected cases (Fig. 1). This is a highly significant increase ($P < 0.001$) compared to the number of cases expected for a normal population, i.e. based on registry data.

In the control group, 12 leukaemias were found compared to 7.5 expected cases ($P = 0.08$). Further subclassification of the leukaemias in the exposed group showed a predominance for myeloid leukaemias with an increase by a factor of 3.8 (11 cases observed *vs* 2.9 cases expected; $P < 0.001$), whereas lymphatic leukaemias were elevated by a factor of 2.6 (Fig. 2). Acute myeloid leukaemias (AML) showed the largest increase relative to that expected (7 observed *vs* 1.8 expected; $P = 0.003$).

Three cases of chronic myeloid leukaemia (CML) appeared in patients who had been treated rather early (end of the 1940s/middle of the 1950s; see Table 3), while cases of AML were found in patients who had been treated in subsequent years (twice in the mid 1950s, twice at end of the 1950s, twice at the end of the 1960s and one case at the beginning of the 1970s; see Table 4), There have also been two cases of osteomyelosclerosis/-fibrosis and two cases of myelodysplastic syndrome in the exposure group, all of them treated between the mid-1960s and 1970, whereas no such cases have been observed in the controls.

Considering the seven AML cases in the exposed group: four cases were observed in patients treated with 10 injections, each of 1 MBq ^{224}Ra (i.e. a therapy scheme applied until recently); one case in a patient who received 0.6 of this activity; and one case in a patient who received 1.6 times this activity. The one remaining case occurred in a patient with uncertain activity, this is because one series of 20 injections could not be verified. This breakdown indicates that at least five out of the seven AML cases are associated with an activity that has been applied in the therapy until very recently.

Discussion

Current treatment and management recommendations for AS patients [5] comprise an individual combination of non-pharmacological and pharmacological therapies [3, 5]. Non-pharmacological treatment includes education, exercise, physiotherapy, rehabilitation, patient associations and self help groups. NSAIDs are considered as first-line drug treatment (alternative: selective COX-2 inhibitors). Analgesics [e.g. 4-acetamidophenol (paracetamol) and opioids] are recommended for patients in whom NSAIDs are insufficient, contraindicated or not tolerated. Local corticosteroid injections might be considered. However, the systemic use of steroids is not evidence-based. The use of DMARDs, including SSZ and MTX, is not supported by evidence for the treatment of axial disease. However, SSZ is an option for peripheral arthritis. TNF α-blockers are recommended for patients with insufficient improvement under conventional treatment. Typical surgical treatment options comprise total hip arthroplasty and spinal surgery. External beam radiotherapy is no longer part of the internationally accepted recommendations, especially those proposed by a combined 'Assessment in Ankylosing Spondylitis' working group (ASAS) and 'European League Against Rheumatism' (EULAR) task force [5]. However, radiotherapy with ^{224}Ra, using the presented protocol was a widely accepted treatment [15, 19, 30, 31]. Large cohorts of patients who were treated with ^{224}Ra are still alive, and deserve a thorough analysis of their risk of developing malignant diseases as a consequence of their treatment.

Review of the literature only reveals a few investigations studying acute or short-term adverse health effects of ^{224}Ra treatment in AS patients [20–22]. Alberding *et al.* [19] investigated 278 of 399 patients who received ^{224}Ra (total activity 10 MBq) in Germany between 2000 and 2004. They found a good drug tolerance within a 6-month follow-up period. Six adverse events, none of them serious and not leading to discontinuation of the

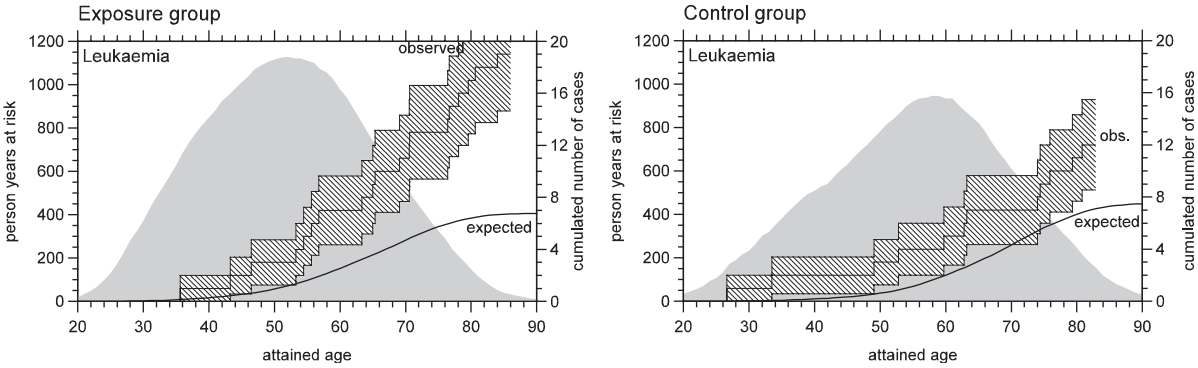

FIG. 1. Leukaemia incidence (all types) in the exposure (left panel) and the control group (right panel). The grey shaded areas give the number of patients under observation as a function of attained age (i.e. the person-years at risk; left ordinate). The step functions with the hatched range of standard errors represent the cumulative number of leukaemia cases (right ordinate); the expected number of cases is indicated by the lower curve.

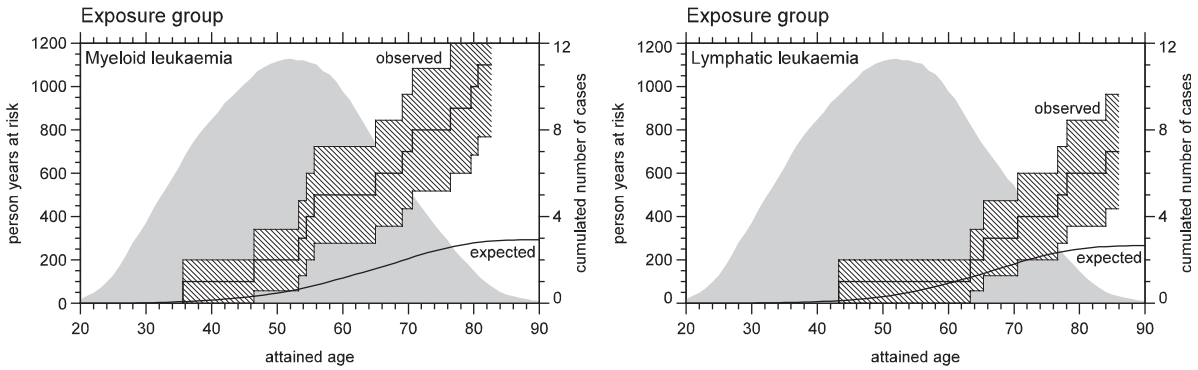

FIG. 2. Observed and expected incidence of myeloid leukaemia (left panel) and of lymphatic leukaemia (right panel) in the exposure group related to attained age (analogous to Fig. 1).

TABLE 3. Chronic myeloid leukaemias in the exposure group

Patient no. (sex)	91 (male)	7004 (male)	7227 (male)
Start of treatment (month, yr)	10,1949	1956[a]/10,1962	1950
Injection span [weeks]	9 ?	12[a]/4	10
Pure ^{224}Ra = 1, peteosthor = 2	2	1	2
Body weight (kg)	55	69	n/a
Injected amount (MBq)	30	12.4[a]/4.2	19.9
Skeletal dose (Gy)	2.07	0.68[a]/0.23	1.07
[month, year] of birth	01.1900	01.1930	10.1900
[month, year] of diagnosis	09.1955	1976	≈1977
Age at death (yrs)	59	50	77
Latency time (yrs)	6	20[a]/14	≈27

[a]Injection series not exactly verified. ?: Injection span not exactly verified.

treatment were documented. The group concluded that treatment of AS with ^{224}Ra was effective.

The present study assesses the long-term effects, after treatment of AS with ^{224}Ra, in a unique way. Reliable results for the risk of leukaemia (with a statistically significant enhancement) could be obtained for humans injected with 0.17 MBq/kg of ^{224}Ra, due to a very long post-treatment observation period of >25 yrs.

In the earlier study by Spiess and co-workers [8–10, 12], the most prominent detrimental side effect of the bone seeking α-emitter ^{224}Ra were 56 malignant tumours of the skeletal region compared to less than one case expected according to cancer registry data. In the present study, an insignificant excess of only four cases of malignant diseases of bone and bone marrow (*vs* 1.8 cases expected) was observed. Even in earlier reported evaluations of the present study cohort these tumours were only marginally elevated ($P = 0.04$) [32–34], and since 1999 no further cases have been reported. However, two of these cases were tumours of the haematopoietic system (one reticulum cell sarcoma of bone marrow and one medullary plasmocytoma), thus potentially indicating a damage of the bone marrow at lower doses of ^{224}Ra. Damages of the bone marrow caused by injected ^{224}Ra have also been previously discussed by other authors [20, 35].

Most striking, however, is the high number of leukaemias observed in the present study. A higher than normal rate of leukaemia in this AS disease group might be expected due to a relatively high consumption of analgesic and antiphlogistic drugs. It is well known that phenylbutazone, a medicament often used in treatment of AS in the past, may cause bone marrow damage [36, 37]. However, the leukaemia excess found here is restricted to the exposed group: 19 cases (*vs* 6.8 expected cases, $P < 0.001$) were observed amongst the 1471 patients of the exposed group (1.3%), whereas only 12 leukaemias occurred amongst the 1324 patients of the control group (0.9%). Six of the seven leukaemias among the exposed as well as among the controls were of chronic lymphatic type (CLL). Recently, there have been indications that CLL may also be radiation-inducible [38], which is in contrast to earlier radioepidemiological assumptions. In the present study, an increase of CLL rates by a factor of about two was observed both in the exposed and in the control group. This may indicate an association of CLL with AS as previously described [39, 40].

Further subclassification of the leukaemias demonstrates a large increase of myeloid leukaemias: although no myeloid leukaemias had been observed in the present study groups before 1981 [25], there has been a continual increase in the exposed group since then. The initial ratio of myeloid leukaemias in exposed:control groups changed from 8:3 in 1999 [27] to 9:3 in 2003 and to 10:3 in 2004, finally reaching 11:4 by the end of 2006. Amongst the 1471 exposed patients we found 11 myeloid leukaemias (0.75%) *vs* only 2.9 expected cases ($P < 0.001$), whereas there were only 4 *vs* 3.1 expected cases of myeloid leukaemia among 1324 controls (0.3%). The increased rate of

TABLE 4. Acute myeloid leukaemias in the exposure group

Patient no. (sex)	1337 (male)	1589 (male)	5109 (male)	5110 (male)	7453 (male)	7810 (male)	4076 (male)
Start of treatment (month, yr)	2, 1953	11, 1973/1977	1953/2, 1957	3, 1957	5, 1959	9, 1968	9, 1968
Injection span (weeks)	9	20[a]/10	16	10	10	6	10
Pure ^{224}Ra = 1, peteosthor = 2	1	1	1	1	1	1	1
Body weight (kg)	69	n/a	75	70	n/a	n/a	n/a
Injected amount (MBq)	8.7	20.7[a]/10.4	15.9	9.1	10.4	6.2	10.6
Skeletal dose (Gy)	0.48	1.12[a]/0.56	0.79	0.50	0.56	0.34	0.58
[month, year] of birth	11, 1921	11, 1946	11, 1904	12, 1909	1, 1926	2, 1919	3, 1931
[month, year] of diagnosis	$\approx$ 1974	7, 1982	6, 1984	8, 1990	1980	2, 1984	11, 2001
Age at death (yrs)	53	35	80	80	65	65	71
Latency time (yrs)	21	23/27	23/27	33	21	15	33

[a]Injection series not exactly verified.

myeloid leukaemia is highly significant, not only when compared with a standard population based on registry data ($P < 0.001$), but also according to a modified Fisher's test. Such a Fisher's test, which takes into account the expected cases in both groups, and thus not only the different sizes of the groups, but also the different age distributions, shows a significant difference ($P < 0.05$) in the direct comparison of the exposed (11 cases observed *vs* 2.9 cases expected) and the control group (4 cases observed *vs* 3.1 cases expected).

It is especially the high number of AML cases that makes the major contribution to the total number of leukaemias in the exposed group (7 cases *vs* 1.8 expected cases, $P = 0.003$). In the control group only three cases of AML compared with 2.0 expected cases were observed. Although AML has been found to be elevated in HLA-B27-positive persons by Au *et al.* [41], not all HLA-B27-positive persons develop AS. Moreover, there may be a different genetic background in the study group of Au *et al.* from the Queen Mary Hospital, Hong Kong, compared with a European population. It is well known that there are certain genetic differences, not only in the prevalence of HLA-B27, but also in its association with AS [42].

The enhanced leukaemia rates reported in the present study are consistent with results from animal studies in which low doses of ^{224}Ra have been demonstrated to induce leukaemia. ^{224}Ra injected at lower doses than those found to cause a maximum yield of osteosarcomas [43] were seen to induce leukaemia instead [44, 45].

In the German Thorotrast study, an elevated number of myeloproliferative diseases has been observed at—compared with the animal experiments—lower dose rates (1.7 mGy/week): 40 cases of myeloid leukaemia *vs* 7 cases in the controls, and 30 cases *vs* 4 cases of myelodysplastic syndrome [46]. However, enhanced numbers of myeloproliferative diseases, mostly being acute leukaemias, have been observed in Thorotrast studies from other countries too [47].

Rheumatology key message

- In a group of patients treated with ^{224}Ra for AS, long-term health effects were investigated. A significantly enhanced leukaemia risk has been observed, especially for myeloid leukaemia.

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