Treatment of Ankylosing Spondylitis with Radium-224-Chloride

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Ankylosing Spondylitis

Osseous-inflammatory ankylosis of the spine of unknown etiology

Course [follow. Koch 1978]
appr. 10% painful, inflammatory
appr. 20% osseous, less painful
appr. 70% mixed pattern, periodic
Therapy

• Simply symptomatically
  - physical therapy, breathing exercise
  - pharmacological therapy
    - antiinflammatory (NSAIDs)
    - analgetic
    - „Basic therapeutics“, Biologicals
  - Radiation / Radionuclide therapy
  - surgical
History

- Ra-224 (Thorium-X)
  - since 1925 in France (Lèri)
  - since 1944 in England (Hernaman-Johnson)
  - since 1948 in Germany (Troch, Pitzen)

⇒ Production ceased for economic reasons at the end of the 80th
"the new" Ra-224

- approved since II / 2000
- pure Radium-224-Chloride
- half life $^{\text{phys.}}$ 3.6 d, half life $^{\text{eff.}}$ ~ 2 d
- decay: 4 $\alpha$ particles (50$\mu$m)
  1 $\beta$ particle (8mm)
  final product appr. 2ng Pb
- excretion: 95% feces, 5% urine
  (40% in 3 days, 94% in 6 days)
Caution !!

• Mistake
  Thorium X = Ra-224 not = Thorotrast
  ➢ Thorium-232 (halflife $1.4 \times 10^9$ y, Tu-Induction)

• former overdose
  ➢ 2x2 MBq/week, months – years (max. 140MBq)
  ➢ > 6% malignant bone tumors

• application in children

• contamination with Eosine and Platine
Principle of action

• incorporation as Ca\textsuperscript{++}-analogue in bone and sites of mineralization
• accumulation below End-/Periosteum and in areas of bone remodeling

... Thus

- reduction of inflammatory response
- decreasing pain
- retardation of ankylosis
Leading to ....

- increasing readiness for physical therapy because of pain
- reduction of NSAIDs or analgesics
- improvement in QoL
- progressive ankylosis is stopped or at least retarded
Therapy schedule

- i.v. injection of 10 x 1MBq RaCl$_2$ once/week
- outpatient treatment
- monitoring of blood counts and parameters of inflammation
- physical examination and 2-phase bone scan, prior to and after treatment
- repeated treatment after 10 years
painful-inflammatory bone remodeling

i.v. injection of Ra-224

incorporation of Ra-224 in bone

Pain palliation, improved mobility

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Indication I

- diagnosis of ankylosing spondylitis
- stage II und III (SIJ + spine)
- pain, parameters of inflammation during antiinflamm. pharmacotherapy („resistant to treatment“)
- progressive ankylosis (spine, chest)
Indication II

• **Cooperation between**
  
  ➢ **Rheumatologist**
  diagnosis, pharmacotherapy, follow-up

  ➢ **Nuclear medicine specialist**
  proof of areas of increased mineralization (bone scanning)
Bone scintigraphy

generally normal blood-pool images
sometimes sacroiliitis

mineralization images with signs of local increase of osteoblast-activity
Contraindications

- gravidity / breast-feeding
- active epiphyseal plates
- recent bone fracture
- hematopoietic diseases
- hepatic dysfunction
- bone marrow depression
- final stage of ankyl. spondylitis (bamboo stick)
- female (male) < 40 years
Bone metabolism in AS

Tc99m-HDP uptake
... is a sensitive measure of altered bone metabolism Holmes 1978, JNM; Fogelman et al. 1978, JNM

• no correlation between bone markers and disease activity of AS!
Inhibition of osteoblasts?

Bone-uptake

- prior to Ra-224: 21,0 ± 3,9%
- after Ra-224: 21,0 ± 3,4%

No direct inhibition of osteoblast activity!
acute side effects

• transient increase in pain
• occasional iridocyclitis

• rarely slight changes in blood counts
• very rarely allergic reactions
• very rarely transient increase of liver enzymes
delayed side effects

• Spiess 1995 😞
  • n=899
  • many < 21 Jahre
  • 1945-1964 partly treated with excessive activities of „Peteosthor“ (up to 140MBq)
  • malignant bone tumors in 6,2% of patients
  min. activity 15MBq Ra-224

• Wick et al. 1995, 1999
  • n=1577, > 21 y.
  • 1948-1975 treated with 10x1MBq Ra-224
  • $\Sigma$ malignant tumors 9,4% (11% control group)
  • no osteosarcoma, two soft-tissue sarcomas
  • 1% hematopoetic malignomas (0,5% c.g.) 😊
Radiation doses Ra-224 (10MBq)

- bone surface 5.4 Gy
- risk of osteosarcoma (animal data) ⇒ statistically increased > 9 Gy
- bone marrow 0.53 Gy
- risk leukemia $2 \times 10^{-3}$/Gy ⇒ $1 \times 10^{-3} = 0.001 = 0.1\%$
- effective whole-body dose 2.74 Sv
Clinical Efficacy

- Historical studies, appr. 2,700 patients, with ~ 75% success
- 4 controlled studies with Ra-224 (n=416), comparison with conventional therapy (n=178) ⇒ 93% improvement (40% c.g.)

Lassmann et al., Rad Environ Biophys 2002
Z Rheumatol 60:84-87 (2001)

- Statement of the German Assoc. of Rheumatol concerning treatment of AS with Ra-224-Cl
  - „proof of principle“ with good effects from historical data in appr. 75%
  - low risk of delayed side effects
  - progression of ancylosis is probably retarded

Demand of long-term phase-IV study (10 y)
Compared to biologicals

- **Etanercept (soluble TNF$\alpha$-receptor)** 2x/week, s.c.
  - $\Rightarrow$ 57% success, 6 months
- **Infliximab (TNF$\alpha$-receptor blocker)** every 6 week i.v.
  - $\Rightarrow$ > 80% success, 12 months

Braun et al., Akta Rheumatol 2002

- recurrence after termination
- **side effects:** infections, allergic reactions, reactivation of tuberculosis, sepsis, tumor recurrence, no long-term experiences!

- **costs:** Infliximab appr. 30,000€/y (Ra224: 1x appr. 6,000€)
Summary

Ra-224 for therapy of ankylosing spondylitis

⇒ is effective
⇒ is easy-to-perform and well tolerated
⇒ carries a low risk of side-effects
⇒ is cost-effective compared with other treatments (biologicals) or their secondary expenses (NSAIDs)

Thank you!