



核医学による悪性腫瘍内用療法の状態

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現在行われている 悪性腫瘍に対する治療

- 手術
- 化学療法
- 放射線療法
- 内用療法 - 限定的
- 免疫療法、….

現在本邦で行われている 悪性腫瘍に対する内用療法

- β 線による治療
- 甲状腺癌： **I-131**
- 様々な癌の骨転移に対する除痛： **Sr-89**
- 悪性リンパ腫： **Y-90**＋抗体
- 神経内分泌腫瘍： **I-131 MIBG** (ノルアドレナリン類似体)

甲状腺癌に対するI-131治療

- 甲状腺分化癌(乳頭癌、ろ胞癌)の
甲状腺全摘術後の再発予防(アブレーション)
残存・遠隔転移に対する治療
- 甲状腺癌の罹患率・死亡率(1.6%・0.4%)は、近年とも増加傾向。
- アブレーション(30mCiまで)は外来治療が可能。

甲状腺癌に対するI-131入院治療

- 厳しい法規制（放射線障害防止法と医療法）と
厳しい診療報酬のため、病院経営の観点から避けられる傾向がある。
- ベッド数は全国で135床（人口94万人あたり1床）
10年間で28%減少。3-6ヶ月の入院待ち。

悪性リンパ腫に対するY-90ゼバリン治療

- CD20陽性のB細胞性悪性リンパ腫が対象。
- Y-90はβ線のみしか放出しないため、外来治療が可能。
- 有用性は高いが、高価。

非放射性薬剤の開発も非常に進んでいる。

海外における内用療法

- β 線放出核種を用いた治療が中心
- 肝腫瘍： Y-90治療
- 神経内分泌腫瘍： Lu-177 (Y-90) 標識ソマトスタチン
アナログ治療
- その他多数

悪性腫瘍に対する α 線内用療法

- 高いエネルギーと短い飛程が特徴
- 短い飛程のために、治療対象病変に近づける工夫が必要。
- 外来治療が可能

前立腺癌に対するRa-223治療

- 骨転移を有する治療抵抗性前立腺癌が対象
- 投与したRa-223が骨に集積し、腫瘍縮小および除痛効果を示す。
- 海外では既に実績あり。
2013年に41 million Euro、2014年前半に79 million Euroの売り上げを記録(バイエル社より)。
- 本邦では治験第2相

Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial

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Summary

Background Bone metastases frequently cause skeletal events in patients with metastatic castration-resistant prostate cancer. Radium-223 dichloride (radium-223) selectively targets bone metastases with high-energy, short-range α -particles. We assessed the effect of radium-223 compared with placebo in patients with castration-resistant prostate cancer and bone metastases.

Methods In this phase 3, double-blind, randomised ALSYMPCA trial, we enrolled patients who had symptomatic

Findings Between June 12, 2008, and Feb 1, 2011, 921 patients were enrolled, of whom 614 (67%) were randomly assigned to receive radium-223 and 307 (33%) placebo. Symptomatic skeletal events occurred in 202 (33%) of 614 patients in the radium-223 group and 116 (38%) of 307 patients in the placebo group. Time to first symptomatic skeletal event was longer with radium-223 than with placebo (median 15.6 months [95% CI 13.5–18.0] vs 9.8 months [7.3–23.7]; hazard ratio [HR]=0.66, 95% CI 0.52–0.83; p=0.00037). The risks of external beam radiation therapy for bone pain (HR 0.67, 95% CI 0.53–0.85) and spinal cord compression (HR=0.52, 95% CI 0.29–0.93) were reduced with radium-223 compared with placebo. Radium-223 treatment did not seem to significantly reduce the risk of symptomatic pathological bone fracture (HR 0.62, 95% CI 0.35–1.09), or the need for tumour-related orthopaedic surgical intervention (HR 0.72, 95% CI 0.28–1.82).

Interpretation Radium-223 should be considered as a treatment option for patients with castration-resistant prostate cancer and symptomatic bone metastases.

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TABLE 1: Clinical Trials That Used α -Particle Therapy

Isotope	Target, Antibody	Cancer Type	Reference
^{213}Bi	CD33, ^{213}Bi -HuM195	Chronic myelomonocytic leukemia	[42–44]
^{213}Bi	CD20, rituximab	Non-Hodgkin lymphoma	[45]
^{213}Bi	Neurokinin type-1 receptor, substance P (11-mer peptide)	Glioblastoma	[46]
^{213}Bi	NG2 proteoglycan, monoclonal antibody 9.2.27	Melanoma	[47]
^{223}Ra	Hydroxyapatite in remodeling bone, $^{223}\text{RaCl}$	Prostate cancer	[1, 48–55]
^{211}At	Untargeted, ^{211}At -human serum albumin	Carcinoma of tongue	[56–58]
^{211}At	Tenascin-C, chimeric 816 antibody	Glioblastoma	[59–61]
^{211}At	^{211}At -MX35 F(ab') ₂	Ovarian carcinoma	[62]
^{225}Ac	^{225}Ac -DOTA, HuM195	Leukemia	[63–65]

Note—HuM195 = humanized monoclonal antibody 195, MX35 = murine monoclonal antibody, F(ab')₂ = fragment antigen-binding, DOTA = tetraazacyclododecanetetraacetic acid.

Table 1. Clinical trials using α -particle emitters

Trial	Cancer type	Radioimmunoconjugate	Outcome	Reference
Zalutsky and colleagues	Glioblastoma	^{211}At -ch81C6	18 patients treated; 14 patients survived 12 mo	27, 28
Andersson and colleagues	Ovarian cancer	^{211}At -MX35-F(ab') ₂	9 patients treated; no significant toxicity	29
The Scheinberg group	AML	^{225}Ac -HuM195 (^{225}Ac -lintuzumab)	18 patients treated; trial expanded to multicenter phase III	31, 32
Heeger and colleagues	B-cell non-Hodgkin lymphoma	^{213}Bi -labeled anti-CD19 and anti-CD20-CHX-A'-DTPA	9 patients treated; 2 patients showed response; limited toxicity in 2 patients	33
The Allen group	Melanoma	^{213}Bi -mAb 9.2.27	22 patients treated; 6% CR; 14% PR; 50% stable disease	34
The Scheinberg group	AML	^{213}Bi -HuM195 (^{213}Bi -lintuzumab)	18 patients treated; 14 patients had reductions in marrow blasts	35
Jurdic and colleagues	AML	^{213}Bi -HuM195 (^{213}Bi -lintuzumab)	31 patients treated; marrow blast reductions observed at all dose levels	36
The Merlo group	Glioblastoma	^{213}Bi -substance P	5 patients treated; Barthel index improved for 2 patients	37, 38
Areva Med LLC	Ovarian	^{212}Pb -TMC-trastuzumab	3 patients treated; study ongoing; no further information available	39
Parker and colleagues	Castration-resistant prostate cancer and bone metastases	Alpharadin (^{223}Ra chloride)	292 patients treated; median overall survival increased by 4.5 mo compared with placebo group	40

NOTE: This is strictly speaking not a TAT trial *per se* but uses $^{223}\text{Ra}^{2+}$. Alpharadin is not an immunoconjugate but is included here because ^{223}Ra is an α -emitter.

Abbreviations: AML, advanced myeloid leukemia; CR, complete response; PR, partial response.

α 線内用療法の普及に向けての課題

- RIの安定かつ低価格での供給
- 安全性の適切な評価
- 抗体あるいはその他のターゲット手法の早期実用化
- 専門的知識を有する医療チームの構築