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Intraperitoneal Radionuclide Therapy – Clinical and Pre-Clinical Considerations

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1. Introduction

For early stage (stage I) epithelial ovarian cancer (EOC) surgery may be the sole curative therapy. However, the vast majorities of cases are diagnosed in more advanced stages and need a multimodal treatment strategy. Therefore, in stage II and higher, surgery with a cytoreductive intent, (i.e. to remove as much as possible the macroscopic disease from the peritoneal surfaces in adjunct to bilateral salpingo-oophorectomy) is not curative by itself, but has to be supplemented by cytotoxic therapy. This is mainly administered as intravenously (i.v.) chemotherapy or sometimes as intraperitoneal (i.p.) chemotherapy. Although there are trials using whole abdominal or moving-strip external beam radiotherapy as adjuvant therapy (Einhorn et al., 2003) or i.p. radiotherapy with colloid preparations of ^{198}Au or ^{32}P (Rosenhein et al., 1979; Varia et al., 2003) these have so far not presented results to merit a place in the normal therapeutic arsenal, and long term toxicity from normal tissues is a major concern.

Despite extensive cytoreductive surgery and modern chemotherapy, with complete remissions (CR) at second look laparotomy (SLL) and normalisation of the serum marker cancer antigen 125 (CA-125), approximately 70% of the patients in stage III recur and will eventually succumb to their disease. The recurrence pattern is normally the development of ascites due to progression of treatment resistant cells growing as peritoneal microscopic deposits. From this incurable situation the progression is dominated by a continuous accumulation of ascites with intestinal adhesions and bowel obstructions. This progression can often be temporarily halted by palliative chemotherapy, or in special occasions, local external beam radiotherapy, but will in any event, eventually lead to a great deal of suffering and pain from above the abdominal cavity pathology.

Since the negative impact on survival and the suffering associated with uncontrolled spread in the abdominal cavity, efforts have been directed to develop more effective local treatments. Such a local more aggressive treatment strategy has proven effective as chemotherapy injected locally in the peritoneal cavity (i.p.) could show as a reduction in recurrences and a decrease in mortality, although at the expense of clearly increased toxicity (Jaaback & Johnson, 2009). The use of ^{90}Y, conjugated to a monoclonal antibody (mAb) and studied in a large prospective randomised controlled study, unfortunately did not demonstrate a benefit (Oei et al., 2007; Verheijen et al., 2006).

These negative results on overall survival of i.p. radioimmunotherapy (RIT) using the β-emitter ^{90}Y, conjugated to a mAb, are a concern (Verheijen et al., 2006), even if a decreased local i.p. recurrence has been seen (Oei et al., 2007). A number of important issues relating to this trial including the physical properties of the used nuclide will be discussed in depth, which might give clues to optimization of future trials of intraperitoneal RIT.

2. Radionuclides

In targeted radionuclide therapy the cytotoxic effect is mediated by a radionuclide, brought to the target by the targeting construct (Elgqvist et al., 2010). Below is a list of the radionuclides used, in both animal and clinical studies. The list includes a presentation of their physical characters, and in which studies they have been used.

^{225}Ac (Actinium-225). ^{225}Ac decays with a half-life of 10 days and emits four α-particles in a serial decay. The α-particle emitted from ^{225}Ac has an energy of 5.8 MeV (mean linear energy transfer [LET] ≈ 120 keV/μm) and the daughters are ^{221}Fr ($T_{½}$ = 4.8 min, E = 6.3 MeV, mean LET ≈ 118 keV/μm), ^{217}At ($T_{½}$ = 32.3 ms, E = 7.1 MeV, mean LET ≈ 109 keV/μm), and ^{213}Bi ($T_{½}$ = 45.6 min, E = 8.4 MeV, mean LET ≈ 99 keV/μm). The α-decays are accompanied by gamma(γ)-radiation, enabling scintigraphy and dosimetry. ^{225}Ac has been used in one animal study (Borchardt et al., 2003).

^{211}At (Astatine-211). ^{211}At (an α-particle emitter) is cyclotron produced via the nuclear reaction ^{207}Bi(α,2n)^{211}At. ^{211}At decays with a half-life of 7.2 hours in 2 ways: (*i*) via emission of an α-particle (E = 5.9 MeV) to ^{207}Bi, or (*ii*) via an electron capture process to ^{211}Po. ^{207}Bi decays with a half-life of 31.6 y to ^{207}Pb (stable). ^{211}Po decays with a half-life of 0.5 s to ^{207}Pb via α-particle emission (E = 7.4 MeV). The 5.9- and 7.4-MeV α-particles have a mean LET of ~122 and ~106 keV/μm and a particle range in tissue of ~48 and ~70 μm, respectively. The decays are accompanied by γ-radiation, enabling scintigraphy and dosimetry. ^{211}At has been used in animal studies (Andersson et al., 1999, 2000a, 2000b, 2001; Bäck et al., 2005; Elgqvist et al., 2005a, 2005b, 2006a, 2006b, 2006c, 2009a, 2009b; Steffen et al., 2006) and in one clinical study (Andersson et al., 2009).

^{213}Bi (Bismuth-213). ^{213}Bi (an α-particle emitter) is available via a generator based technology due to its relatively long-lived parent radionuclide, ^{225}Ac. ^{213}Bi decays with a half-life of 45.6 min to ^{209}Bi (stable) during which it emits an α-particle of 8.4 MeV (mean LET and particle range in tissue: ~99 keV/μm and ~89 μm, respectively). The α-particle emission is accompanied by γ-radiation. ^{213}Bi has been used in animal studies (Knör et al., 2008; Song et al., 2007).

^{90}Y (Yttrium-90). ^{90}Y is chemically similar to the lanthanoids and decays with a half-life of 64 h by the emission of electrons (β) with a maximum energy of ~2.2 MeV (E_{mean} = 933 keV). The emitted electrons have a maximum range in tissue of ~12 mm (mean range ≈ 4 mm) and a mean LET ≈ 0.2 keV/μm. Due to the emission of *Bremsstrahlung,* scintigraphy is feasible. ^{90}Y has been used in one animal study (Buchsbaum et al., 2005) and in clinical studies (Alvarez et al., 2002; Epenetos et al., 2000; Grana et al., 2004; Hird et al., 1990; Hnatowich et al., 1988; Maraveyas et al., 1994; Oei et al., 2007; Rosenblum et al., 1999; Stewart et al., 1990; Verheijen et al., 2006).

^{177}Lu (Lutetium-177). This radionuclide has a half-life of 6.7 d and decays by the emission of β-particles with a maximum energy of 497 keV (E_{mean} = 133 keV), which have a range in tissue of ~2 mm (mean range ≈ 0.2 mm), and a mean LET < 0.1 keV/μm. It also emits γ-radiation (208 keV). ^{177}Lu can be produced in large scale owing to the high thermal

neutron capture cross-section of ^{176}Lu (2100 barn) using moderate flux reactors. ^{177}Lu has been used in animal studies (Buchsbaum et al., 1999, 2005; Persson et al., 2007; Tolmachev et al., 2007) and in clinical studies (Alvarez et al., 1997; Epenetos et al., 1987; Meredith et al., 1996, 2001).

^{131}I (Iodine-131). ^{131}I has a half-life of 8 d and decays by the emission of β-particles with a maximum energy of 807 keV (E_{mean} = 182 keV, mean LET ≈ 0.1 keV/μm), which have a maximum range in tissue of ~3.6 mm (mean range ≈ 0.4 mm). It emits γ-radiation (364 keV) enabling scintigraphy and dosimetry. ^{131}I has been used in animal studies (Kievit et al., 1996; Molthoff et al., 1992; Turner et al., 1998) and in clinical studies (Buchsbaum et al., 1999; Buijs et al., 1998; Buist et al., 1993; Colcher et al., 1987; Crippa et al., 1995; Epenetos et al., 1987; Mahé et al., 1999; Molthoff et al., 1992, 1997; Muto et al., 1992; Stewart et al., 1989a, 1989b; Van Zanten-Przybysz et al., 2000, 2001).

^{186}Re (Rhenium-186) and ^{188}Re (Rhenium-188). ^{186}Re has a half-life of 3.7 d and decays by emitting β-particles having a maximum energy of 1.07 MeV (mean LET ≈ 0.1 keV/μm), 90% of it delivered within ~1.8 mm. ^{186}Re also emits γ-radiation. ^{186}Re has been used in clinical studies (Breitz et al., 1995; Jacobs et al., 1993). ^{188}Re has a half-life of 17 h and decays by emitting β-particles having a maximum energy of 795 keV (mean LET ≈ 0.1 keV/μm). The emitted γ-radiation enables scintigraphy and dosimetry. ^{188}Re has been used in one clinical study (Macey & Meredith, 1999).

3. Targeting constructs

In developing treatment strategies against EOC based on the concept of targeted radionuclide therapy several candidates as targeting constructs have been evaluated. Below follow a compilation of the main targeting constructs that have been used for bringing the radionuclide to the target, in animal as well as in clinical studies.

HMFG1 is a murine monoclonal antibody (mAb) which is directed to an epitope of the MUC1 gene product. MUC1 is a large, heavily glycosylated mucin (>400 kDa) expressed on the apical surface of the majority of secretory epithelial cells (Gendler, 2001). MUC1 is overexpressed in 90% of adenocarcinomas, including cancers of the ovary (Mukherjee et al., 2003). The extracellular portion of the MUC1 protein mainly consists of a variable number of highly conserved 20 amino acid repeats (Verheijen et al., 2006). HMFG1 has been used in clinical studies (Epenetos, et al., 1987; Verheijen et al., 2006).

HMFG2 is a murine mAb that is directed towards a large mucin-like molecule normally produced by the lactating breast. The mAbs react with similar components expressed by the majority (>90%) of ovarian, breast and other carcinomas (Arklie, et al., 1981). The HMFG2 epitope is generally expressed at a higher level in tumors (Burchell et al., 1983). HMFG2 has been used in one clinical study (Epenetos et al., 1987).

AUA1 is a murine IgG1 mAb that binds to an antigen expressed by a wide range of adenocarcinoma, including the majority (>90%) of carcinomas of the ovary. The antigen is a 40 kDa glycoprotein (Epenetos et al., 1982). AUA1 has been used in one clinical study (Epenetos et al., 1987).

H17E2 is a murine IgG1 mAb that is directed to placental and placental-like alkaline phosphatase (PLAP) (Travers & Bodmer, 1984). This enzyme is expressed as a surface membrane antigen (~67 kDa) of many neoplasms, including 60%–85% of ovarian carcinomas (Benham et al., 1978; Sunderland et al., 1984). H17E2 has been used in one clinical study (Epenetos et al., 1987).

Hu2PLAP is a human IgG1 κ mAb that has the same specificity as the murine H17E2 mAb described above. Hu2PLAP has been used in one clinical study (Kosmas et al., 1998).
H317 is a murine IgG mAb developed after immunisation with syncytiotrophoblast microvilli preparations from term placenta. It is specific for the *L*-phenylalanine inhibitable placental alkaline phosphatase (PLAP). H317 has been used in one clinical study (Kosmas et al., 1998).
Trastuzumab (Herceptin; Genentech, South San Francisco, CA) is a humanized IgG1 mAb that recognizes the extracellular domain of the HER-2/*neu* oncoprotein (Carter et al., 1992). Trastuzumab has been used in one animal study (Borchardt et al., 2003).
Pertuzumab is a human mAb binds to the dimerization domain II of HER-2. Pertuzumab is based on the human immunoglobulin IgG1 κ framework sequences, and is produced in Chinese hamster ovary cells. It has been used in one animal study (Persson et al., 2007).
B72.3 is a murine mAb that has been shown to be immunoreactive with the glycoprotein complex TAG-72 (>200 kDa) with the characteristics of a mucin (Johnson et al., 1986; Thor et al., 1986; Wolf et al., 1989). TAG-72 expression has been shown in the majority of ovarian carcinomas tested (Nuti et al., 1982). B72.3 has been used in clinical studies (Colcher et al., 1987; Rosenblum et al., 1999).
CC49 is a murine mAb is a high-affinity murine product that reacts with the tumor-associated glycoprotein TAG-72, which is expressed by the majority of common epithelial tumors (Schlom et al., 1990). CC49 has been used in one animal study (Buchsbaum et al., 2005) and in clinical studies (Alvarez et al., 1997, 2002; Buchsbaum et al., 1999; Macey et al., 1999; Meredith et al., 1996).
OC125 is a murine mAb that is directed against the tumor marker CA-125, and has been used in clinical studies (Hnatowich et al., 1988; Mahé et al., 1999; Muto et al., 1992).
MOv18 is a murine mAb that recognizes and reacts with a surface antigen, which is a membrane folate-binding glycoprotein of 38 kDa expressed on approximately 90% of all human ovarian carcinomas (Boerman et al., 1991; Campbell et al., 1991; Miotti et al., 1987). MOv18 (murine and in some cases chimeric) has been used in animal studies (Andersson et al., 1999, 2000a, 2000b, 2001) and in clinical studies (Buijs et al., 1998; Buist et al., 1993; Molthoff et al., 1992, 1997; Van Zanten-Przybysz et al., 2000, 2001).
MX35 is a murine IgG1 mAb directed towards a cell-surface glycoprotein of ~95 kDa on OVCAR-3 cells (Welshinger et al., 1997) and is expressed strongly and homogeneously on ~90% of human epithelial ovarian cancers (Rubin et al., 1993). The antigen recognized by MX35 is characterized as the sodium-dependent phosphate transport protein 2b (NaPi2b) (Yin et al., 2008). MX35 F(ab')2 has been used in animal studies (Bäck et al., 2005; Elgqvist et al., 2006a, 2006b, 2006c, 2009a, 2009b) and in one clinical study (Andersson et al., 2009).
NR-LU-10 is a IgG2b murine mAb that is reactive with a glycoprotein (~40 kDa) expressed on most carcinomas of epithelial origin (Goldrosen et al., 1990; Varki et al., 1984). NR-LU-10 has been used in clinical studies (Breitz et al., 1995; Jacobs et al., 1993).
A5B7 is an anti-CEA IgG1 mAb that has been used in one large-animal model (sheep) study (Turner et al., 1998).
17-1A is a chimeric mAb is directed towards a ~39 kDa membrane-associated pancarcinoma glycoprotein (Edwards et al., 1986; Koprowski et al., 1979). It has been used in one animal study (Kievit et al., 1996).
323/A3 is a murine mAb that is directed to a ~39 kDa membrane-associated pancarcinoma glycoprotein (same as 17-1A) (Edwards et al., 1986; Koprowski et al., 1979). It has been used in one animal study (Johnson et al., 1986).

hCTMO1 is an antibody that was constructed by taking the short hypervariable regions of the murine mAb CTMO1 and grafting them into a human IgG4. It is directed towards a glycoprotein expressed on malignant cells of epithelial origin (Baker et al., 1994; Zotter et al., 1988). hCTMO1 has been used in one clinical study (Davis et al., 1999).
OV-TL 3 is a murine IgG1 mAb that recognizes a cell-surface antigen highly expressed on >90% of ovarian carcinomas (Poels et al., 1986). It has been used in one clinical study (Buist et al., 1995).
139H2 is a IgG1 mAb which binds to a protein determinant of episialin (Hilkens et al., 1988). 139H2 has been used in one animal study (Molthoff et al., 1992).
P-P4D is a targeting construct which is a pseudo-symmetrical covalent dimer of the monomeric peptide P-P4. It has been used in one animal study (Knör et al., 2008).
PAI2 is a targeting construct that is a plasminogen activator inhibitor type 2 and which is a member of the serine protease inhibitor (Serpin) superfamily and forms SDS-stable 1:1 complexes with urokinase plasminogen activator (uPA) (Song et al., 2007). It has been used in one animal study (Song et al., 2007).
Affibody molecules are composed of alpha helices and lack disulfide bridges. Two such molecular constructs, $(Z_{HER2:4})_2$ and $(Z_{HER2:342})_2$ (~15 kDa) have been used in animal studies (Steffen et al., 2006a, 2006b; Tolmachev et al., 2007).

4. Labeling chemistry

In nuclear medicine targeted therapy all to date approved radiopharmaceuticals are based on β-particle emitters. However, an increasing interest has been focused on α-particle emitting radionuclides as they offer several advantages over the most commonly used β-emitters for the treatment of micro-tumors. Unlike medically applied therapeutic radionuclides that decay by medium- to high-energy β-particle emissions leading to low-LET radiation with particle ranges varying from 1 to 10 mm, α-particle emitting radionuclides emit high-LET radiation in a small volume determined by the α-particle ranges of 50–100 μm. Only a few α-emitters fulfill the criteria for endoradiotherapeutic applications, the most studied being ^{211}At, ^{212}Bi, and ^{213}Bi. All these nuclides decay by 100% α-particle emission. Astatine-211 decays in two branches, 58% probability through electron capture to ^{211}Po which in turn decays through an α-particle emission (7.45 MeV) with a half-life of 0.52 seconds to the stable ^{207}Pb. The other branch (42%), resulting in an α-particle of 5.87 MeV, also ends in the stable ^{207}Pb through the daughter ^{207}Bi. The decay of ^{212}Bi is very similar to the decay of ^{213}Bi in terms of half-life and energy emitted ($T_{½}$ for ^{212}Bi = 60.6 min versus $T_{½}$ for ^{213}Bi = 45.6 min, mean E_{α} of both nuclides ≈ 8–8.5 MeV). However, while ^{213}Bi can be isolated as pure nuclide from the ^{225}Ac/^{213}Bi generator, ^{212}Bi is obtained *in situ* from the decay of ^{212}Pb. Lead-212 decays to ^{212}Bi with a half-life of 10.6 h.
For stable attachment of metals such as ^{212}Pb/^{212}Bi or ^{213}Bi to tumor specific targeting constructs an intermediate bifunctional chelating agent is required. A number of different chelating derivatives have been developed for conjugate labeling of various carrier molecules. Biological targeting constructs such as antibodies and peptides are commonly labeled with metal nuclides via chelating agents based on DTPA (diethylenetriaminepentaacetic acid) or DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid). Heat sensitive proteins are preferably labeled with the semi rigid open chain DTPA derivatives, e.g. CHX A``DTPA, due to the fast metal coordination reaction kinetics at room temperature. DOTA is a versatile chelating agent which shows strong

binding to a number of different metals, and the rigid structure give a metal-complex stronger than that of the corresponding complex to DTPA. However, chelating a metal to DOTA require heat or microwave assisted reaction condition, to be completed in reasonable times and with good yields, and are therefore more suitable for labeling to small molecules and peptides (Cordier et al., 2010).

The most common functional leaving group of the reagent is succinimidyl ester which is directed towards free amines on proteins and peptides, mainly presented on the side chain of lysine. For example, an antibody of IgG class has a molecular weight of approximately 150 kDa, and contains approximately 1200 amino acids, of which a number of lysine is randomly distributed. A lysine directed reagent conjugated to the antibody will therefore be non-specifically distributed in the protein structure, occasionally including the active antigen binding sites. Consequently the antigen binding capacity of the antibody may be affected when using lysine amine binding reagents. Site specific conjugation of antibodies can be achieved by targeting the sulfhydryl group on the side chain of cystein. In antibodies, cystein form disulfide bridges at specific sites within the antibody distant from the antigen binding site. The disulfide bridges can chemically be gently disrupted resulting in conjugate sites for a labelling reagent, e.g. malemido reagents. In this way the antigen binding of the conjugated antibody will not be compromised.

Independent of chelating moiety the procedure for labeling is conjugation of the chelating derivative to the carrier molecule and then labeling to the conjugate. The direct chelating of the metal nuclide to the conjugate is a prerequisite when labeling with metal nuclides with very short half-lives, e.g. ^{213}Bi. The other α-emitting isotope of bismuth ^{212}Bi is generated in the decay of ^{212}Pb. Generally ^{212}Pb or a mixture of ^{212}Pb/^{212}Bi is bound to a DOTA conjugate targeting construct. However, it has been reported that a fraction will be dechelated in the decay of ^{212}Pb, leaving a free fraction of ^{212}Bi (Su et al., 2005).

Compared with the ^{213}Bi, ^{211}At is perhaps the most versatile mainly because of its longer half-life, 7.2 h, which allow time for radiolabeling and quality control, and the time to distribute to the target cancer cells. Astatine is the heaviest element in the halogen family and since its discovery in 1940 (Corson et al., 1947) it has been proposed for use in nuclear medicine applications. Several research and preclinical studies utilising ^{211}At for therapeutic nuclear medicine applications have been conducted, including the free halide, and ^{211}At-labeled tumor specific targeting constructs (Zalutsky et al., 2000). Many of these studies include tumor specific monoclonal antibodies, as they constitute suitable carrier properties for a number of different malignancies (Anderson et al., 2000b). Encouraging preclinical results have been obtained in radioimmunotherapy with astatinated antibodies and two phase I studies have emerged from these studies (Andersson et al., 2009; Zalutsky et al., 2008). However, ^{211}At requires a medium energy cyclotron for its production which is a major obstacle hampering clinical studies. And of the available cyclotrons having the capacity to produce ^{211}At, only a few of those facilities actually produce ^{211}At. Of the available cyclotrons having the capacity to produce ^{211}At, only a few of those facilities actually produce ^{211}At. In addition, one of the most demanding challenges in ^{211}At-radioimmunotherapy applications has been the development of adequate chemical labeling procedures for the production of ^{211}At-labeled antibodies at clinical levels of activity. Unlike direct iodination of proteins, astatine cannot be stably attached to unmodified antibodies (Visser et al., 1981). A number of different bifunctional labeling reagents for astatination of proteins have therefore been developed in which the common feature involves an electrophilic substitution reaction of organic tin as leaving group in the formation of an aryl-carbon- astatine bond, and a functional group for binding to proteins,

commonly N-succinimidyl esters (Wilbur et al., 1989; Yordanov et al., 2001; Zalutsky et al., 1988). The radiochemistry is in general conducted in two steps, labeling of the reagent and conjugation of the labeled reagent to antibody. However, when using this strategy problems with yields and the final quality are frequently occurring, and have been recognised being due to radiolytic effects within the reacting solvents (Pozzi et al., 2007). Especially at high activity concentration conditions the α-particle decay of astatine may during labeling result in a considerable absorbed dose to the reaction solvent which can affect the chemistry, i.e. self-oxidation of astatine, decompose the precursor and/or alter the structural and biological integrity of the antibody. In fact, it has been reported that antibodies can be subjected to a maximum absorbed dose of approximately 1000 Gy without affecting its immunoreactivity (Larsen & Bruland, 1995).

Similar to metal radiolabeling, in which a bifunctional chelate is conjugated to the protein prior to labeling, the ATE reagent can be conjugated to the protein prior to astatination. In this way problems related to absorbed dose to reaction volumes, and dependency on protein concentration, can be avoided. The resulting yield and specific activities can be kept high even at high activity reaction conditions (Lindegren et al., 2008). However, although stable *in vitro* it has been found that the aryl-carbon-astatine bond is not stable *in vivo* when bound to small carrier molecules, e.g. antibody fragments such as F(ab)-fragments and minibodies.

Based on the higher strength of boron-astatine bonds (Kerr, 1977), new bifunctional reagents based on boron-cage structures, *nido*-carborane and *closo*-decaborate(2-) have been developed to increase the *in vivo* stability of astatination of biomolecules (Wilbur et al., 2004, 2009). The rout for synthesis of astatinated antibodies and fragments with the boron-cage reagents is, as the in metal radiolabeling, conjugation of the reagent to the antibody and subsequently direct radiohalogenation of the immunoconjugate. Halogenation yields are therefore generally higher than the yields obtained in two step astatination of the ATE reagents. Greater stability to dehalogenation of the astatinated products labeled via boron-cage chemistry has been confirmed (Wilbur et al., 2004).

5. Animal studies

Several animal studies investigating radionuclide therapy have been performed during the past couple of years. They have been investigating the pharmacokinetics, toxicity and therapeutic efficacy. The studies presented below comprise a selection of these studies using different radionuclides as well as different targeting constructs, and are paragraphed based on which radionuclide have been used, i.e. ^{225}Ac, ^{211}At, ^{213}Bi, ^{90}Y, ^{177}Lu, or ^{131}I. Some of the studies are not in an intraperitoneal setting, but have been mentioned because of their importance and relevance.

5.1 ^{225}Ac-Trastuzumab

One study has investigated the immunoreactivity, internalization, and cytotoxicity using SKOV-3 cells (Borchardt et al., 2003). The immunoreactivity was retained (50%–90%) and the radioimmunocomplex internalized into the cells (50% at 2 h). Various therapies were evaluated, using unlabeled trastuzumab and 8.1, 12.2, or 16.6 kBq of ^{225}Ac-trastuzumab or ^{225}Ac-labeled control antibody. The therapies were given 9 d after tumor inoculation. Groups of control mice and mice administered unlabeled trastuzumab had median survivals of 33, 37 or 44 d, respectively. The median survival was 52–126 d using ^{225}Ac-trastuzumab, and 48–64 d using the ^{225}Ac-control mAb. Some deaths from toxicity occurred at the highest

activity levels. The study showed that i.p. administration of ^{225}Ac-trastuzumab extended survival in mice at levels that produce no apparent toxicity. An advantage of ^{225}Ac is that it emits a cascade of α-particles, implying a very high cytotoxic effect if the α-particle emissions occur in close vicinity to the cancer cell nuclei. The disadvantage is that when ^{225}Ac decays it will be separated from its targeting construct, making the remaining emitted α-particles an unspecific irradiation that potentially could lead to both dosimetry and toxicity problems. ^{225}Ac should therefore be used with caution in situations other than for example during intracavitary treatments or when the radioimmunocomplex is relatively rapid internalized into the cancer cells.

5.2 ^{211}At-MOv-18, ^{211}At-MX35 and ^{211}At-Affibody

Astatine-211 is a very promising radionuclide due to its half-life of 7.2 h and short particle range (~70 μm). A drawback is its limited availability due to the fact that it is cyclotron produced, and only a few cyclotrons world-wide produce ^{211}At today. The potential problem with unspecific irradiation (as described above for ^{225}Ac) is negligible due to the fact that the α-particle emanating from the second decay route (from ^{211}Po to ^{207}Pb) occurs with a very short half-life (0.5 seconds), i.e. in close vicinity to the targeted cancer cell (Palm et al., 2004). Andersson et al. have performed studies investigating the pharmacokinetics and therapeutic efficacy of ^{211}At-labeled mAbs (Andersson et al., 1999, 2000a, 2000b, 2001). In one of those studies the purpose was to compare the therapeutic efficacy of ^{211}At-MOv18 and ^{131}I-MOv18 (Andersson et al., 2001). The study used OVCAR-3 cells growing i.p. in mice. Two weeks after the i.p. inoculation of 1×10^7 tumor cells twenty mice were treated i.p. with MOv18 labeled with either ^{211}At (310–400 kBq) or ^{131}I (5.1–6.2 MBq). The pharmacokinetics of the labeled antibody in tumor-free animals was studied and the resulting absorbed dose to bone marrow was estimated. When the mice were treated with ^{211}At-MOv18 nine out of ten mice were free of macro- and microscopic tumors compared to three out of ten when ^{131}I-MOv18 was used. The equivalent dose to bone marrow was 2.4–3.1 Sv from ^{211}At-MOv18 and 3.4–4.1 Sv from ^{131}I-MOv18. The study showed that the therapeutic efficacy of ^{211}At-MOv18 was high, and superior to that using ^{131}I-MOv18.

Other studies using ^{211}At-mAbs have also been completed (Bäck et al., 2005; Elgqvist et al., 2005a, 2005b, 2006a, 2006b, 2006c, 2009a, 2009b). In one of those studies the purpose was to estimate the efficacy of RIT using ^{211}At-MX35 F(ab')2 or ^{211}At-Rituximab F(ab')2 (non-specific) against differently sized ovarian cancer deposits on the peritoneum, and to calculate absorbed dose to tumors and critical organs (Elgqvist et al., 2006a). At 1–7 w after inoculation animals were i.p. treated with ~400 kBq ^{211}At-MX35 F(ab')2, ~400 kBq ^{211}At-Rituximab F(ab')2, or unlabeled Rituximab F(ab')2. Eight weeks after each treatment the mice were sacrificed and the presence of tumors and ascites was determined. When given treatment 1, 3, 4, 5, or 7 w after cell inoculation the tumor-free fraction (TFF) was 0.95, 0.68, 0.58, 0.47, 0.26, and 1.00, 0.80, 0.20, 0.20, and 0.0 when treated with ^{211}At-MX35 F(ab')2 or ^{211}At-Rituximab F(ab')2, respectively. The conclusion of the study was that treatment with ^{211}At-MX35 F(ab')2 or ^{211}At-Rituximab F(ab')2 resulted in a TFF of 0.95–1.00 when the tumor radius was ≤30 μm. The TFF was decreased (TFF ≤ 0.20) for the non-specific ^{211}At-Rituximab F(ab')2 when the tumor radius exceeded the range of the α-particles. The tumor specific mAb resulted in a significantly better TFF, for different tumor sizes, explained by a high mean absorbed dose (>22 Gy) from the activity bound to the tumor surface, probably in addition to some contribution from penetrating activity.

Another study (although not i.p.) evaluated the relative biological effectiveness (RBE) of ^{211}At-mAb (Bäck et al., 2005). The endpoint was growth inhibition (GI) of subcutaneous OVCAR-3 xenografts. The animals received i.v. injections of ^{211}At-MX35 F(ab')2 (0.33, 0.65, and 0.90 MBq). External irradiation of the tumors was performed with a ^{60}Co source. To compare the biologic effects of the two radiation qualities, the mean value for GI was plotted for each tumor as a function of its corresponding absorbed dose. Exponential fits of these curves were made, and the absorbed doses required for a GI of 0.37 (D_{37}) were derived, and also the RBE of ^{211}At was determined. Absorbed doses in tumors were 1.35, 2.65, and 3.70 Gy. D_{37} was determined to 1.59 ± 0.08 Gy (mean ± SEM). Tumor growth after irradiation by the ^{60}Co source resulted in a D_{37} of 7.65 ± 1.0 Gy. The RBE of ^{211}At irradiation was calculated to be 4.8 ± 0.7 Gy.
In yet another study (also not i.p.) HER-2 binding affibody molecules were labeled with ^{211}At, using the PAB and a decaborate-based linker, and the biodistribution in tumor bearing mice was investigated (Steffen et al., 2006a). Compared with a previous biodistribution with ^{125}I, the ^{211}At biodistribution using the PAB linker showed higher uptake in lungs, stomach, thyroid and salivary glands, indicating release of free ^{211}At. When the decaborate-based linker was used, the uptake in those organs was decreased, but instead, high uptake in kidneys and liver was found. The conclusion of the study was that affibody molecules have suitable blood-kinetics for targeted radionuclide therapy with ^{211}At, the labeling chemistry however affects the distribution in normal organs to a high degree and needs to be improved to allow clinical use.

5.3 ^{213}Bi-P-P4D and ^{213}Bi-PAI2

Bismuth-213 has a well established chemistry, is available via a generator, and has recently achieved an increased attention. A drawback is its short half-life (45.6 min), which necessitates a rapid specificity, once injected. Using ^{213}Bi in intracavitary or i.p. applications, or using pretargeting techniques, could however overcome this potential problem. A study using ^{213}Bi has been performed by Knör et al. developing peptidic radioligands, which targets cancer cell urokinase receptors (uPAR, CD87) (Knör et al., 2008). DOTA-conjugated, uPAR-directed ligands were synthesised. Biodistribution of ^{213}Bi-P-P4D was analysed in mice 28 d after i.p. inoculation of OV-MZ-6 ovarian tumor cells in the absence or presence of the plasma expander gelofusine. Binding of ^{213}Bi-P-P4D to monocytoid U937 and OV-MZ-6 cells was shown using the natural ligand of uPAR, pro-uPA, or a soluble form of uPAR, suPAR, as competitors. The ^{213}Bi-P-P4D showed superior binding to OV-MZ-6 cells *in vitro*, and accumulation of ^{213}Bi-P-P4D in tumor tissue was shown by biodistribution analysis in mice bearing i.p. OV-MZ-6-derived tumors. Gelofusine reduced the kidney uptake of ^{213}Bi-P-P4D by 50%. In conclusion, ovarian cancer cells overexpressing uPAR were specifically targeted *in vitro* as well as *in vivo* by ^{213}Bi-P-P4D, and the kidney uptake was reduced by gelofusine.
An additional study also using ^{213}Bi has been published by Song et al. in which they investigated the pharmacokinetics, toxicity and *in vivo* stability of ^{213}Bi-PAI2, and also determined if a prior injection of the metal chelator Ca-DTPA or lysine would reduce the toxicity by decreasing the renal uptake (Song et al., 2007). Two different chelators (CHX-A"-DTPA and cDTPA) were used for the preparation of the ^{213}Bi-PAI2 conjugate; for i.p. administration in mice and ear vein injection in rabbits. Neither the mice nor the rabbits displayed any short term toxicity over 13 w at 1,420 MBq/kg and 120 MBq/kg ^{213}Bi-PAI2, respectively. The kidney uptake was markedly decreased (threefold) by blocking with lysine. Nephropathy caused by radiation was observed at 20–30 w in the mice, whereas severe renal tubular necrosis was detected at 13 w in the rabbits. In conclusion, the

nephropathy was the dose-limiting toxicity, and lysine was effective in reducing the uptake in the kidneys. Maximum tolerated doses were 350 and 120 MBq/kg for the mice and rabbits, respectively. The same research group has earlier shown the *in vitro* cytotoxicity and *in vivo* inhibition of tumor growth in breast, prostate, pancreatic, and ovarian cancer (Allen et al., 2003; Li et al., 2002; Qu et al., 2005; Ranson et al., 2002; Song et al., 2006).

5.4 ^{90}Y(or ^{177}Lu)-DOTA-biotin-streptavidin-CC49

Owing to efforts at developing strategies for RIT against ovarian cancer (Alvarez et al., 2002) the same research group also investigated pretargeted RIT in an i.p. tumor model (LS174T) using four CC49 anti-tumor-associated glycoprotein 72 (TAG-72) single-chain antibodies linked to streptavidin as a fusion protein (CC49 fusion protein) (Buchsbaum et al., 2005). A synthetic clearing agent was administered i.v. one day later to produce hepatic clearance of unbound CC49. A low molecular weight radiolabeled reagent composed of biotin conjugated to the chelating agent 7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) complexed with ^{111}In-, ^{90}Y-, or ^{177}Lu was injected four hours later. The radiolocalization to tumor sites was superior with i.p. administration of radiolabeled DOTA-biotin as compared to i.v. administration. Imaging and biodistribution studies showed good tumor localization with ^{111}In- or ^{177}Lu-DOTA-biotin. Tumor localization of ^{111}In-DOTA-biotin was 43% ID/g (percentage of injected dose per gram) and 44% ID/g at 4 and 24 hours with the highest normal tissue localization in the kidney with 6% ID/g at 48 and 72 h. ^{90}Y-DOTA-biotin at doses of 14.8–22.2 MBq or ^{177}Lu-DOTA-biotin at doses of 22.2–29.6 MBq produced significant prolongation of survival compared with controls ($p = 0.03$ and $p < 0.01$). The conclusion of the study was that pretargeted RIT using regional administration of CC49 fusion protein and i.p. ^{90}Y- or ^{177}Lu-DOTA-biotin is a therapeutic strategy in the LS174T i.p. tumor model and that this strategy may be applicable to humans. LS174T is a human colon cancer cell line, but as it was used in an i.p. setting in this study together with CC49 (which reacts with the tumor-associated glycoprotein TAG-72, expressed by the majority of common epithelial tumors) we think it is relevant to present the results.

5.5 ^{177}Lu-Pertuzumab and ^{177}Lu-Affibody

Lutethium-177-Pertuzumab has been used for disseminated HER-2-positive micrometastases (Persson et al., 2007), and showed good targeting in mice bearing HER-2-overexpressing xenografts. Absorbed radiation dose in tumors was more than 5 to 7 times higher than that in blood and in any normal organ. ^{177}Lu-Pertuzumab delayed tumor progression compared with controls (no treatment, $p < 0.0001$; Pertuzumab, $p < 0.0001$; and ^{177}Lu-labeled irrelevant mAb, $p < 0.01$). Adverse side effects of the treatment could not be detected. In conclusion, the results support the possibility using ^{177}Lu-Pertuzumab in clinical studies.

In a study by Tolmachev et al. a ^{177}Lu-labeled anti-HER-2 affibody molecule ($Z_{HER2:342}$) targeting xenografts was used (Tolmachev et al., 2007). Due to the small size (~7 kDa) of the affibody molecule rapid glomerular filtration and high renal accumulation occurred. Reversible binding to albumin reduced the renal excretion and uptake though. The affibody molecule $(Z_{HER2:342})_2$ (i.e. dimeric) was fused with the albumin-binding domain (ABD) conjugated with the isothiocyanate derivative of CHX-A''-DTPA and thereafter labeled with ^{177}Lu. Fusion with ABD caused a 25-fold reduction of the renal uptake in comparison with the non-fused dimer molecule $(Z_{HER2:342})_2$. The biodistribution showed high uptake of the conjugate in HER-2-expressing tumors. Treatment of SKOV-3 microxenografts (having a high HER-2 expression) with 17 or 22 MBq ^{177}Lu-CHX-A''-DTPA-ABD-$(Z_{HER2:342})_2$ prevented

formation of tumors completely. In LS174T xenografts (having a low HER-2 expression), this treatment resulted in a small but significant increase of the survival. In conclusion, fusion with ABD improved the *in vivo* biodistribution and indicated ^{177}Lu-CHX-A''-DTPA-ABD-$(Z_{HER2:342})_2$ as a candidate for the treatment of disseminated tumors having high HER-2 expression.

5.6 ^{131}I-A5B7

In a large animal study of human tumors in cyclosporin-immunosuppressed sheep, by Turner et al., evaluation and measurement of tumor uptake of ^{131}I-mAbs was done (Turner et al., 1998). Human cancer cells were orthotopically inoculated (~10^7 cells): SKMEL melanoma subcutaneously; LS174T and HT29 colon carcinoma into bowel, peritoneum and liver; and JAM ovarian carcinoma into the ovary and peritoneum. The tumor xenografts grew within 3 w and generally maintained their histological appearance, a few tumor deposits showing some degree of dedifferentiation though. Regional lymph node metastases were shown for xenografts from the melanoma and ovarian carcinoma. An anti-CEA mAb (A5B7) labeled with ^{131}I was administered intravenously. The peak uptake at 5 d in orthotopic tumors in the gut was 0.027% ID/g and 0.034% ID/g in hepatic metastases with tumor-to-blood ratios of 2.0–2.5. The non-specific uptake in melanoma tumors was 0.003% ID/g. In conclusion, the uptake of ^{131}I-mAb in human tumors was comparable to the uptake observed in patients, and this sheep model may therefore be more realistic than mice xenografts for prediction of the efficacy of RIT.

6. Clinical studies

Several clinical protocols have been reported on during the past twenty years, although almost all of them have been small phase I radiopharmaceutical biokinetics and absorbed dose-finding studies (Alvarez et al., 2002; Jacobs et al., 1993; Macey et al., 1999; Meredith et al., 1996, 2001; Van Zanten-Przybysz et al., 2000,2001), or phase I/II studies with no controls or at best matched historical cases (Epenetos et al., 1987, 2000; Hird et al., 1990; Nicholson et l., 1998; Stewart et al., 1989a, 1989b). Tumor stage and degree of advanced disease have varied greatly between, and also within, these studies as have the used targeting constructs and the choice of radionuclide. Albeit, these studies are important as they have provided us with the necessary starting hubs to the scaffold of knowledge that needs to be acquired. The major exception from this is the only randomised phase III study reported by Verheijen et al. (Verheijen et al., 2006). Despite its negative results it still holds as the major publication so far on intraperitoneal (i.p.) radioimmunotherapy for ovarian cancer and also stresses the importance of performing randomized studies. This study was spurred by the positive findings in a non-randomized phase I/II trial (Epenetos et al., 2000; Nicholson et al., 1998), where prolonged disease free and long term survival was described after one i.p. treatment, using ^{90}Y labeled murine HMFG1 antibody, in patients that had received a complete response on standard treatment (surgery and primary chemotherapy). Prior to these reports, a few other small clinical studies using different radionuclides and targeting constructs, had likewise suggested a possibly better treatment effect of i.p. radioimmunotherapy, correlating inversely with size of residual disease; ^{131}I (Epenetos et al., 1987; Crippa et al., 1995; Stewart et al., 1989a, 1989b); and ^{186}Re (Jacobs et al., 1993).

Thus, the Verheijen study (Verheijen et al., 2006) finally recruited 447 patients between February 1998 and January 2003, with ovarian cancer (FIGO stage Ic-IV) to evaluate if a single i.p. infusion of 25 mg of the β-particle emitter ^{90}Y conjugated to the murine HMFG1

antibody could prolong survival in patients in complete clinical response (physical examination and CT-scan and CA-125) after surgical debulking and finishing standard platinum containing chemotherapy and, importantly, with a macroscopically negative second-look laparoscopy. However, contrary to the beliefs from the pre-studies this large prospective randomized study failed to demonstrate any survival benefit. Using Cox proportional hazards analysis of survival, no difference was found, after a median follow-up of 3.5 years 70/224 patients had died in the active treatment arm compared with 61/223 in the control arm. Also time to relapse was similar between groups and 104/224 active treatment patients experienced relapse compared with 98/223 of controls.

Although the study was carefully planned and well conducted and performed one should consider the following points which could have contributed to conceal positive effects of the active treatment. A) Peritoneal adhesions in up to an entire quadrant did not exclude patients in this study, which could potentially result in a significant underdosing of ≤ 25% of the abdominal cavity. Further, the adhesions were assessed by laparoscopy, CT scan or isotope diffusion scan, where only the latter can allow a solid enough assessment of adhesions and to discern between one or two quadrants of adhesions. Importantly, it is unclear if patients (no adhesions versus one quadrant with adhesions) were stratified between each treatment arm. B) A possible skewing of patients with more advanced disease characteristics to the treatment arm is evident, e.g. in the active treatment arm there were 8% more patients with residual disease after initial surgery (44.2% vs. 35.9%) and there were 3% more stage III and IV patients in the treatment arm which also had a higher mean CA-125 level after laparoscopy (never explained). Furthermore, 7% more patients in the standard arm received consolidation chemotherapy (19.7% vs. 12.5%). C) Regarding the radioimmunocomplex and their antigenicity towards the cancer cells one may note that the overall antibody mass of 25 mg may have been insufficient to provide a concentration gradient to help "push" the radiolabeled antibody into the tumors. This can be contrasted to the 250 mg/m^2 of cold antibody used with Zevalin or the 450 mg total antibody dose used with Bexxar. As a multi-center study the radiolabeling process was by necessity performed by each institution and although a radiolabeling efficiency of 95% was confirmed with thin-layer chromatography, a potential loss of affinity of the antibody for the antigen, as a result of the radiolabeling process was not addressed. And lastly; D) The impact of a ≤60% MUC1 staining for 18% of the patients in the treatment arm is grossly unknown.

Although no survival benefit for ^{90}Y-HMFG1 i.p. instillation as consolidation treatment for epithelian ovarian cancer was found, an improved local control of i.p. disease was reported on in a pattern of failure analysis (Oei et al., 2007). Of the 104/224 treatment arm and 98/223 control arm relapses, there were significantly fewer i.p. (40 vs. 69, $p < 0.05$) and more extraperitoneal (47 vs. 13, $p < 0.05$) relapses in the treatment arm. Correspondingly, time to i.p. recurrence was significantly longer (53.4 vs. 46.4 months, $p = 0.0019$) and time to extraperitoneal recurrence was significantly shorter for the treatment arm (51 vs. 63.6 months, $p < 0.001$).

Thus, the main negative result of the Verheijen study balances back somewhat, in that, some treatment effects can be seen locally i.p. with a delaying of local relapses which, however, could not translate into an effect on survival. Bearing in mind the above listed concerns, it is from our research group's perspective (the Targeted Alpha Therapy Group, www.TAT.gu.se), tempting to argue that the failure of the treatment could simply be explained by the choice of radionuclide, i.e. when treating microscopic disease with high energy β-particles emitted from ^{90}Y, the electron will have too long a range in order to

deliver high enough energy to the cancer cell nuclei. It has been modelled that high energy β-particle emissions will not deposit large amounts of radiation energy into small microscopic tumor spheroids.

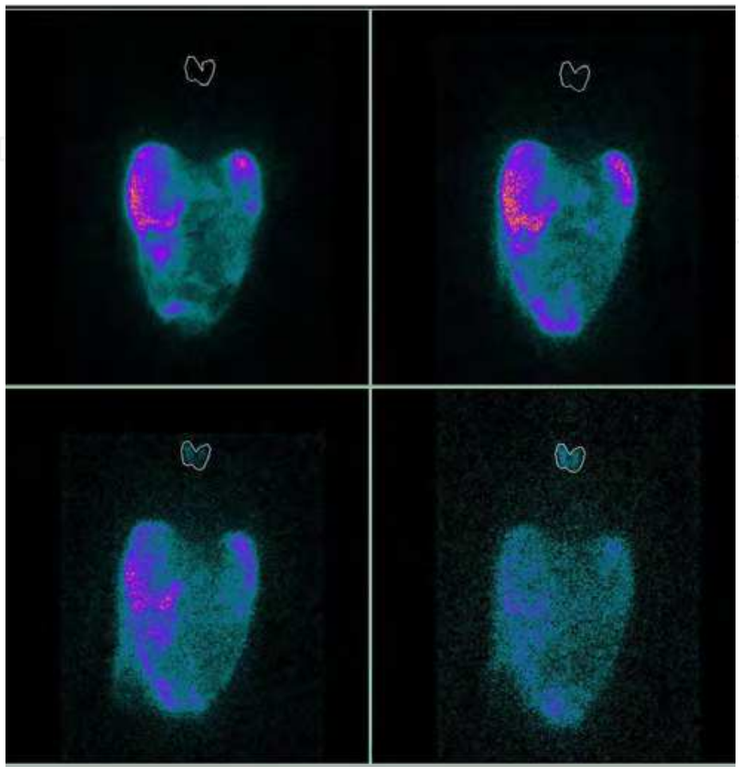

Fig. 1. Consecutive anteroposterior decay corrected scans (γ-camera) of the abdominal and thoracic area of a patient in the study by Andersson et al., 2009. The thyroid uptake, which is indicated by a region of interest in each panel, was not blocked in this patient. Images were acquired at 1.5 (top left), 5 (top right), 11.5 (bottom left), and 19.5 (bottom right) hours after infusion of ^{211}At-MX35 F(ab')2. The figure is reprinted by permission of the Society of Nuclear Medicine from Andersson H, Cederkrantz E, Bäck T, et al. Intraperitoneal α-particle radioimmunotherapy of ovarian cancer patients: pharmacokinetics and dosimetry of ^{211}At-MX35 F(ab´)2 – a phase I study. J Nucl Med 2009;50:1153–1160.

So far, the only clinical study using an α-particle emitter, ^{211}At, for treating ovarian cancer has been performed at our institution (Andersson et al., 2009). In a phase I study the pharmacokinetics and toxicity of α-RIT using ^{211}At- MX35 F(ab')2, in 9 patients with relapsed ovarian cancer was studied after 2nd or 3rd line of chemotherapy. Laparoscopy to exclude presence of macroscopic tumor growth or adhesions was performed prior to infusion with 20.1–101 MBq (0.54–2.73 mCi)/L ^{211}At-MX35 F(ab')2 via a peritoneal catheter. The study demonstrated that it is possible to achieve therapeutic absorbed doses in microscopic tumors without significant toxicity using up to 101 MBq. The potential thyroid toxicity of ^{211}At could be successfully blocked by potassium perchlorate/iodide, (unblocked thyroid, 24.7 ± 11.1 mGy/(MBq/L); blocked thyroid, 1.4 ± 1.6 mGy/(MBq/L)). Two patients have no evidence of disease at 39 and 72 months. A multicenter, phase II study is currently being planned, intended as an upfront adjuvant treatment for a patient population that has received cytoreductive surgery and chemotherapy.

6.1 Tolerability and toxicity

Generally the side effects have been mild, maximum tolerated doses (MTD) depends both on the nuclide used and the specific construct. The highest used activities can be infused using ^{131}I constructs up to 5–6 GBq have been infused using different antibodies, but due to a long half-life (8 days) the bone marrow suppression have been evident (Epenetos et al., 1987; Crippa et al., 1995; Stewart et al., 1989a, 1989b). The long half-life and gamma emission are also a concern regarding the unintentional irradiation of staff, relatives and other patients. In modelling bone marrow absorbed doses (Buchsbaum et al., 1999) using the CC49 antibody, and based on limiting the bone marrow absorbed dose to 2 Gy, the maximum possible administered activity of each of the following radionuclide was calculated: ^{188}Re: 6.2 GBq (167.6 mCi), ^{166}Ho: 4.1 GBq (110.8 mCi), ^{177}Lu: 3.9 GBq (105.4 mCi), ^{186}Re: 2.6 GBq (70.2 mCi), ^{131}I: 2.2 GBq (59.5 mCi), and ^{90}Y: 1.3 GBq (35.1 mCi). Thus, ^{188}Re was found to deliver the lowest RM absorbed dose, primarily because it had the shortest half-life, whereas ^{90}Y delivered the highest RM dose (high energy, long path-length).

For ^{90}Y a variation in MTD depending on the used antibody, from 370 MBq with B72.3 (Rosenblum et al., 1999) up to 895 MBq with CC49 (Alvarez et al., 2002) is described. Prior to the large phase III study, a MTD of 685 MBq was found (Hird et al., 1990; Maraveyas et al., 1994; Stewart et al.,1990) for ^{90}Y using the HFG1-antibody with the bone marrow as dose limiting organ. Subsequently an activity of 666 MBq was used (Nicholson et al., 1998; Verheijen et al., 2006), the most common side effects of nausea, fatigue, arthralgia, myalgia and abdominal discomfort were transient and mainly mild. The expected bone marrow toxicity was evident as thrombocytopenia with as much as 24% of the patients experiencing more than grade 3 toxicity, peeking at 6 weeks after treatment and a few cases 2,4% lasting until 6 months after treatment (Verheijen et al., 2006).

Two combined modality treatment protocols have been reported with subcutaneous IFN α2b and i.p. paclitaxel (100 mg/m^2), combined with i.p. ^{90}Y-CC49, MTD of 895 MBq, (Alvarez et al., 2002) or i.p. ^{177}Lu-CC49-RIT (Meredith et al., 2001). The addition of IFN increased hematologic toxicity such that the MTD of the combination with ^{177}Lu-CC49 was 1.5 GBq/m^2 compared to 1.7 GBq/m^2. Considering the much shorter range of the emitted β-particles from ^{177}Lu (mean range ≈ 0.2 mm) compared to those emitted from ^{90}Y (mean range ≈ 4 mm), ^{177}Lu theoretically has a higher therapeutic index than ^{90}Y for a microscopic disease, due to its ability to more specifically irradiate the tumor cells while sparing healthy tissue.

Strategies to increase the tumor activity and decrease the activity in dose limiting organs have been tested also in small clinical studies. Firstly, data have been presented using EDTA as an effective myeloprotective drug to suppress the bone uptake (Rosenblum et al., 1999). Continuous i.v. infusion of EDTA immediately before i.p. administration of up to 1,665 MBq ^{90}Y-B72.3 presented the expected dose-limiting toxicities of thrombocytopenia and neutropenia but at a higher MTD, and analysis of biopsies demonstrated that the bone and marrow content of the ^{90}Y was 15-fold lower (<0.001% ID/g) in the group receiving EDTA infusion. Secondly, the concept of pretargeted RIT based on the avidin-biotin system, was evaluated in 38 patients (Grana et al., 2004). A three-step protocol: biotinylated mAbs and avidin were i.p. injected (first and second step), and 12–18 h later ^{90}Y-biotin (either i.v. or i.p.) was injected as the third step. Sixteen were treated by i.p. injection only, whereas 22 patients received the combined treatment (i.v. + i.p.), doses ranged from 370 to 3,700 MBq of ^{90}Y-biotin. Both regimens were well tolerated, but two patients showed temporary grade III–IV hematologic toxicity. In conclusion, excellent tolerability and a good potential therapeutic role of pretargeted RIT in advanced ovarian cancer.

7. Radiation dosimetry in the clinical situation

Dosimetry is needed to optimize the amount of radiopharmaceutical that should be administered to the patient (Palm et al., 2011). This involves estimating the maximum administered radioactivity possible at which critical normal organs reach an acceptable degree of toxicity. Dosimetric calculations are mostly only needed for a few critical normal organs. Derived organ absorbed radiation doses, combined with the knowledge about tolerance absorbed doses, provide a guide for estimating the maximum tolerable activity (MTA) that should be given. This approach has been applied in the therapy with β-particle–emitting radiopharmaceuticals when tolerance absorbed doses for critical normal organs have been established. An example is the therapy with ^{177}Lu-octreotate, in which the administered activity is based on dosimetry for the kidneys (Garkavij et al., 2010). The clinical experience with β-particle emitters and estimation of tolerance absorbed doses could possibly be used to predict the outcome for the therapy with α-particle emitters. A first correction should then be made for the higher relative biological effectiveness (RBE) of α-particles. In the first clinical studies, an RBE of 5 has been applied for the estimation of equivalent absorbed doses (Andersson et al., 2009; Bruland et al., 2006; Sgouros et al., 1999). The concept of RBE and the uncertainties of its precise value for α-particles are still under debate and investigated. The weighting factors applied for the estimation of the effective absorbed dose (where a factor of 20 often is recommended by regulators for α-particle radiation) should not be used for predicting therapeutic efficacy and toxicity in patients undergoing radionuclide therapy. These weighting factors were conservatively derived for the stochastic effects and were never meant for use in estimating the deterministic effects relevant for therapy. The clinical experience using α-particles is still very limited, and no tolerance absorbed radiation doses in humans have been determined yet. The current knowledge is therefore limited to *in vitro* and *in vivo* studies. For current and planned clinical studies of α-particle–emitting radiopharmaceuticals, it is therefore very important to gain more insight into the toxic effects of α-particles and its relationship to absorbed dose for different organs. The tolerance absorbed doses found for α-particles could then gradually become established and used for the treatment planning of patients.

Besides the special challenges regarding α-particles, the establishment of pharmacokinetic data for dosimetry calculations does not differ from that of the more conventional β-particle therapies. Nuclear medicine imaging is often used for the quantification of the dosimetric calculations. Much software have been developed for the calculation of the absorbed radiation doses to organs and tumors based on serial 3D imaging and anatomical information from computed tomography (CT) or magnetic resonance imaging (MRI) (Sgouros et al., 2008). Accurate quantification of γ-camera and positron-emission tomography (PET) images and measurements of for example the radioactive blood content over time, are also becoming increasingly important for many diagnostic nuclear medicine procedures. Repeated sample measurements using, for example, a gamma-well counter can provide valuable pharmacokinetic data that allow for accurate absorbed dose calculations. Blood and urine sampling is often possible for patients undergoing therapy. Repeated sampling of peritoneal fluid has also been reported (Andersson et al., 2009). In principle, measurements or images of biopsies from organs of interest would be valuable (Bäck et al., 2010), but the increased dosimetric accuracy gained must be weighed against the discomfort such invasive procedures cause the patient. Simple, non-invasive methods using uptake probes can also provide important information on the pharmacokinetics for an individual

patient. Gaze et al. have demonstrated the usefulness of such an approach for patient dosimetry following ^{131}I-MIBG treatments (Gaze et al., 2005).

Imaging using a γ-camera is commonly used for quantifying the biodistribution of therapeutic radiopharmaceuticals. A prerequisite, of course, being the presence of emitted γ-photons, characteristic X-ray, or bremsstrahlung radiation. The image quality depends on photon energy, photon yields, energy settings, and appropriate matching of collimator and photon energy. The decay chains of the α-particle emitters used hitherto in clinical studies (^{225}Ac, ^{213}Bi, ^{211}At, and ^{223}Ra) all include emissions of photons useful for γ-camera imaging. However, the spatial resolution of γ-camera images is inferior to what is needed to resolve activity distributions within organ compartments or in small tumors. Administered activity and the presence of photons are also much lower compared to the diagnostic situation, resulting in a low signal-to-noise ratio. The possibility of serial γ-camera imaging of patients receiving α-particle therapy is therefore limited for providing quantitative data for dosimetry of whole organs. Low count rates make the preferred 3D SPECT (three dimensional single photon-emission computed tomography) imaging of the radionuclide distribution very time consuming. Serial imaging might therefore be restricted to planar imaging with possibly lower accuracy for the quantification of radioactivity. Such planar images can provide useful quantitative information, and the accuracy can also be increased by using co-registration with CT images (Sjögren et al., 2002).

A focus committee of the Society of Nuclear Medicine provided a review in 1995 of the different factors affecting quantitative SPECT (Rosenthal et al., 1995). The field has developed since then, but the main factors that affect the quantification using SPECT remain the same. Many factors influence the accuracy of the quantification of PET/CT images and include: correction for attenuation, noise, image resolution, and ROI (region of interest) definitions (Alessio et al., 2010; Boellard et al., 2004; Kinahan et al., 1998). Regarding all quantifications, it can be very useful to perform phantom measurements mimicking the patient situation as good as possible. Measurements of that kind can help in selecting the parameters for imaging or probe sessions as well as providing indications of the accuracy that possibly can be obtained (He et al., 2005).

7.1 Tumor and critical organ absorbed doses

Although the maximum amount of administered activity possible is directly related to the absorbed radiation dose to the critical organs, the therapeutic efficacy is determined by the absorbed dose to the tumors. If a low tumor absorbed dose can be expected, the therapy might not be justified. The tumor absorbed dose should therefore, if at all possible, be estimated before treatment. The visualization and quantification using a γ-camera can at best give an estimate of the radiopharmaceutical uptake in the organ as a whole and in large tumors. The determination of absorbed radiation dose to sub-organ compartments or to small tumors or infiltrate cancer cells is though seldom possible.

Estimating the absorbed dose to tumors following α-particle therapy is particularly difficult. Because the targeted tumors often are too small to be detected, at best indirect methods can be used for approximating the absorbed radiation dose. Using antibody or peptide-based therapies, this approximation can for example involve *in vitro* studies on the binding kinetics to antigens or receptor sites for the relevant cancer cell type. Using radionuclides having a decay chain including α-particle–emitting daughters, studies would involve investigating the retention of daughter radionuclides on or in the vicinity of the cancer cells.

Microdosimetry based on such *in vitro* studies could then provide the basis for investigations of the probability for eradicating or stopping or retarding the growth of the tumors. The theoretical basis for such dosimetry has recently been described by Sgouros et al. (Sgouros et al., 2011).

The complexity of the studies and calculations involved for the absorbed dose is considerable, particularly when translating the results to the individual patient for an outcome prediction. This initial complexity should not though prevent formulation of a first, although perhaps rough, estimate. Such estimates, including best-guess information on tumor spread and overall tumor burden, targeting ability, and the amount of delivered radioactivity, will often provide good insight into the potential usefulness of the treatment approach.

As for radionuclide therapies using β-particle emitters, the absorbed dose to critical organs often determines the MTA. The common aim should therefore be to maximize the administered activity to near the level of toxicity for these organs, even for therapies using α-particles. Therapy planning should include calculation of expected organ absorbed doses (Gy) per administered activity (Bq) to identify the optimal amount of activity to be administered. The absorbed dose calculations can either be based on pharmacokinetic data from previous patients or preferably, data from the specific patient is used. Such data could be generated by tracer studies of the actual radiopharmaceutical or a substitute with similar pharmacokinetics. If a fractionated or repeated therapy is to be used, the generation of pharmacokinetic data from each administration should be used for re-planning the remainder. However, differences can arise in the pharmacokinetics between the therapeutic radiopharmaceutical and the tracer or between subsequent therapy sessions, and methods should therefore be established to detect such changes.

7.2 General considerations

The clinical studies using targeted α-particle therapy have their origin in previously established strategies involving β-particle emitters. It is assumed that the significantly shorter track range of the α-particles compared to β-particles provides a therapeutic advantage in that the critical normal organs to a high degree will be spared and a higher absorbed radiation dose to microscopic tumors will be reached. An illustration of this fact is ^{223}Ra therapy for example, in which the bone marrow is less irradiated compared to therapies using β-particle emitters. Radium-223 binds to the skeleton, resulting in a high absorbed dose to the bone surfaces while the absorbed radiation dose to the bone marrow remains relatively low. Consequently, the hematologic toxicity is therefore limited.

If shifting from a β- to an α-particle emitting radiopharmaceutical, the dosimetry differs not only due to the different particles emitted but also due to differences in half-lives and the biokinetics of the free radionuclide. When, for example, using ^{211}At-conjugates, ^{211}At can be set free and be taken up in the thyroid as a result of the natrium iodine symporter (NIS) receptor expressed at the thyroid cells. This process is very similar to that which occurs when iodine-based conjugates are used and iodine is set free and taken up by the NIS receptor. In both of the clinical studies using ^{211}At, blocking agents like potassium perchlorate were used to reduce the uptake in the thyroid cells. This method is well known for iodine-based therapies, and both the normal uptake of iodine in the thyroid and the blocking effect of, for example, potassium iodide are well established. Regarding ^{211}At, the blocking effect can not be considered well established, and careful monitoring is therefore necessary for any unwanted uptake in the thyroid despite the use of blocking agents.

The physical half-life of α- and β-particle emitters used should ideally be matched with the kinetics of the targeting approach. The relatively short half-lives of the α-particle emitters ^{211}At and ^{213}Bi could in general be a disadvantage therefore, but are a good match for the loco-regional therapies such as intraperitoneal. Most of the decays will occur within the intraperitoneal cavity before the substance is distributed throughout the body. To be able to achieve optimal therapeutic efficacy the maximum safe amount of activity should be administered to the patient. The determination of the MTA is typically sought for a patient population but should ideally be estimated for each individual patient as mentioned above; thus, patient-specific dosimetry is needed.

Taking a control image with an analogue is relevant for ovarian cancer. In this case, it is important to determine if the infused radiopharmaceutical can disperse throughout the peritoneal cavity and access all potential microscopic tumors on the peritoneal lining. Leakage control, i.e., determining the lymphatic flow out from the peritoneal cavity, can also be done using an analogue by monitoring the activity concentration in blood over time. Such control images helps manage bone marrow absorbed doses. Pharmacokinetic data show that the variation in absorbed dose to bone marrow among patients is around 20% (Andersson et al., 2009). If the absorbed dose to the bone marrow determines the MTA, then a tracer study could be used to estimate the patient-specific MTA. However, since the peritoneum might determine the MTA for intraperitoneal therapy, only the activity concentration in the peritoneal fluid is probably needed to establish it. In this particular situation, the same activity concentration in the injected solution for all patients can be reasonable, but it is valid only if the patients are free from ascites at the time of injection.

The phase I study on ovarian cancer has generated interest in an adjuvant-targeted α-particle therapy of earlier-stage cancer patients (Andersson et al., 2009). This population would by necessity include patients who would remain disease-free even without the adjuvant therapy. In such settings, it is relevant to include stochastic and/or long-term risks such as secondary cancers and dysfunction of the peritoneum in the justification for the therapy. In this particular case, it is advised that calculation of the equivalent doses to all relevant organs is done, including a conservative estimation of the RBE for α-particles.

8. Future perspectives

The mortality of EOC has not decreased during the past decades, despite a decline in incidence and an intensification of treatment has occurred. The majority of the patients are diagnosed at an advanced stage and most of them will therefore succumb, suffering from abdominal complications. Using present diagnostics, the screening for early stage EOC has not been successful, but efforts in finding proteins in serum indicating early EOC is a vision for future improvements in ovarian cancer survival. Additional approaches are for example the development of targeted treatments, resulting hopefully in higher efficacy and lower toxicity than present day treatments, some of which have been discussed above. Such targeted therapies could include substrate analogues, ligands, or antibodies, resulting in up-regulation of receptors or surface antigens. Antibodies may exhibit a therapeutic effect on their own or as conjugates to toxins or radionuclides. Since the clinical situation is dominated by spread and complications in the abdominal cavity, such therapeutic techniques are primarily directed intraperitoneally. A successful intraperitoneal therapy may eradicate abdominal disease and complications, however, extraperitoneal metastases

may become revealed. Therefore, a combination of abdominal and systemic modalities is most likely required.

As the current available standard treatments often fail to cure a micrometastatic disease, RIT, using short ranged high efficiency α-particles emitted from for example ^{211}At or ^{213}Bi and depositing the radiation energy in close vicinity of the targeted cancer cells, is an attractive approach, possibly in combination with β-particle emitters aimed at larger tumor cell clusters. Such procedures could then be given as a boost after initial cytoreductive surgery and systemic chemotherapy, primarily intraperitoneally but possibly also intravenously by pretargeting approaches, based for example on the avidin/streptavidin-biotin system. A systemic adjunctive approach may be of particular value if the disease includes retroperitoneal vascularized metastases to the lymph nodes for example (Buchsbaum et al., 2005; Frost et al., 2010; Paganelli et al., 1993). Another important concept that could potentially improve the therapeutic index would be to use fractionated RIT, expectedly resulting in decreased normal tissue toxicity while retaining the therapeutic efficacy (Elgqvist et al., 2009b). Auger emitters could also offer an alternative to the radionuclides mentioned above, due to the emitted electrons being low energy (<< 1 keV), and therefore having a very short path length in tissue. To effectively damage the DNA the Auger emitter has to be incorporated into the DNA molecule though, a biological challenge that has to be taken into account for this type of treatment.

The potential disadvantages with a treatment given intraperitoneally are: the i.p. catheter could cause pain and discomfort for the patient, the catheter could leak (and possibly therefore decreasing the therapeutic efficacy and causing a radiation protection problem for the staff), and it could cause an infection and therefore a risk of peritonitis. In order for the i.p. treatments to be successful, especially when using radionuclides that emit short-range particles such as α-particles, loculation and/or adhesions are undesirable and could decrease the therapeutic efficacy. The potential problems of toxicity (especially bone marrow, kidney, peritoneum) and HAMA response always needs to be addressed. A number of review articles have recently been published, regarding RIT in general and RIT against intraperitoneal EOC in particular (Allen, 2004, 2008; Andersson et al., 2003; Chérel, 2006; Crippa, 1993; Gadducci et al., 2005; Gaze, 1996; Goldenberg, 2002; Goldenberg & Sharkey, 2006; Imam, 2001; Kairemo, 1996; Kassis et al., 1996; Meredith et al., 2007; Mulford et al., 2005; Muto & Kassis, 1995; Oyen et al., 2007; Sharkey & Goldenberg, 2005; Zalutsky et al., 2007).

Many different parameters could influence the intraperitoneal therapeutic outcome, some of which are: the specificity of targeting construct, the degree of antigenic expression (Moltoff et al., 1991), loss of immunoreactivity of the targeting construct, amount of unlabeled antibody, diffusion barriers for penetration of the targeting construct into cancer cell clusters, the choice of radionuclide (half-life and particle range), low specific radioactivity, and tumors located extraperitoneally. If treating a microscopic disease the choice of using β-particle emitters could be problematic due to the inability of the β-particles to deliver high enough radiation energy to the target volume, i.e. the cancer cell nuclei. That is probably the reason why the clinical studies performed so far using β-particles have failed when trying to treat microscopic diseases.

The proof-of-concept using an intraperitoneal treatment has been shown in a phase III study by the Gynecologic Oncology Group that included women undergoing initial therapy for advanced ovarian cancer (Armstrong et al., 2006), and the advantage of i.p. compared to i.v. administration for the localization of radiolabeled mAbs to microscopic peritoneal disease

has been shown in some studies, both in animal models and for humans (Andersson et al., 2003; Horan Hand et al., 1989; Ward et al., 1987). Finally, in order to be able to compare and evaluate different treatment strategies the need to conduct randomized, controlled, multicenter clinical studies with large enough patient numbers, enabling statistical significance to occur, must be emphasized and aimed at.

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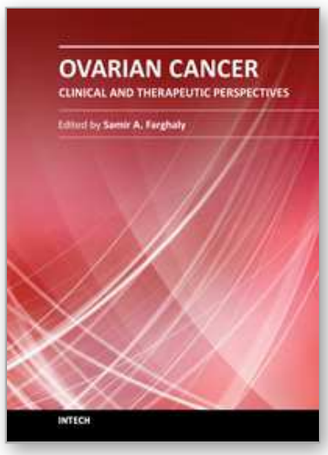

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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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