Kinetics, quantitative analysis and radioimmunolocalisation using indium-111-HMFG1 monoclonal antibody in patients with breast cancer

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Summary

HMFG1 tumour associated monoclonal antibody IgG1 and F(ab')2 fragments were radiolabelled with indium-111 and used to study patients with breast cancer. In vitro and in vivo stability of the radiolabelled antibodies was shown to be satisfactory. Thirty patients with primary breast cancer underwent tumour resection and quantitative evaluation of the radioactivity in the tumour and normal tissues following administration of specific and non-specific antibodies. The mean tumour uptake of HMFG1 F(ab')2 fragments at 24 h was significantly higher (P<0.05) than the intact IgG but at 48 h there was no difference.

Radioactivity in the tumour was predominantly associated with the specific antibody. Nineteen patients with primary or metastatic breast cancer were investigated by external body scintigraphy using HMFG1 F(ab')2 fragments. Successful localisation was observed in approximately 50% of the primary and metastatic lesions with no false positive results. All the patients had observable concentration of 111In in the liver (20% of the injected dose), the kidneys and the spleen. Following i.v. administration, F(ab')2 fragments cleared from the blood more rapidly than the intact IgG. We conclude that HMFG1 F(ab')2 fragments can localise specifically and faster than intact IgG in breast cancer but the sensitivity of the radioimmunoscintigraphy is relatively low. This method needs further improvement before becoming clinically useful for detecting and staging breast cancer.

Radio-labelled monoclonal antibodies raised against human tumour associated antigens have been shown to localise preferentially to tumours, both clinically and in experimental animals (Mach et al., 1981; Epenetos et al., 1982; Farrands et al., 1982; Granowska et al., 1986). Several investigators have reported successful radioimmunolocalisation of breast cancer (Colcher et al., 1983; Rainsbury, 1984; Kalofonos et al., 1988b), but limitations of this approach are the low absolute amount of antibody reaching the target (Epenetos et al., 1986), the heterogeneity of antigenic expression in tumour cells affecting antibody binding (Buchegger et al., 1983) and the persistence of high levels of blood pool radioactivity which makes tumour radiouimmunodetection difficult. Several methods have been reported to reduce the blood pool activity. Begent et al. (1982) reported that liposomally entrapped second antibody could be used to improve tumour to blood ratios 10-fold in comparison to the primary antibody alone. A second alternative is the use of antibody fragments, enhancing the rate of radioactive antibody removal from the blood so tumour could be visualised earlier (Wahl et al., 1983; Khaw et al., 1984).

In this study we report our experience using 111In-labelled F(ab')2 fragments as well as intact HMFG1 monoclonal antibody in patients with breast cancer. The aim of this study was to investigate kinetics, localising efficiency and specificity of HMFG1 F(ab')2 fragments compared to intact monoclonal antibody.

Patients, materials and methods

Patients

Two groups of patients were studied. The first consisted of 15 patients with primary and/or metastatic breast cancer, who were studied by external body scintigraphy. The patients' ages ranged from 38 to 72 years (mean 53). All the patients received 1mCi of 111In-labelled HMFG1 F(ab')2 fragments as an i.v. bolus over 1 min.

The second group consisted of 30 patients with primary breast cancer who underwent tumour resection 24 or 48 h following administration of specific or non-specific monoclonal antibody. Quantitative evaluation of the radioactivity in primary tumour and normal tissue specimens was possible in these patients. The patients' ages ranged from 43 to 74 years (mean 60). Each patient received an i.v. bolus injection of 0.5 mCi of 111In-labelled antibody.

The average amount of injected protein per patient was 250 μg (range 200-300 μg). All patients gave their written informed consent before entering this study. They were skin tested for hypersensitivity to mouse immunoglobulin. No reactions were detected.

Monoclonal antibodies

HMFG1 Monoclonal antibody HMFG1 (Taylor-Papadimitriou et al., 1981), is a murine IgG1 directed against a mucin molecule which is strongly expressed in lactating breast as well as in a range of neoplasms of epithelial origin such as breast, ovarian, gastrointestinal and non-small cell lung cancer (Arkile et al., 1981). It also reacts weakly with normal non-lactating breast and other normal epithelial tissues. It is, therefore, not tumour-specific but it can be described as a tumour-associated antibody. Purity of the antibody was confirmed by isoelectric focusing (Awdeh et al., 1968) and by polyacrylamide gel electrophoresis (Laemmli, 1976). F(ab')2 fragments were produced by pepsin digestion (Nisonoff et al., 1969) as described elsewhere (Kalofonos et al., 1986c).

4C4 The monoclonal antibody 4C4 (Boniol et al., 1982) is a mouse IgG1 directed against the hepatitis B surface antigen. This antibody does not react with neoplasms of epithelial origin such as breast cancer, or with any other human tissues and was used as a negative control. F(ab')2 fragments of the 4C4 monoclonal antibody were kindly provided by Sorin Biomedica (Saluggia, Italy).

Radiolabelling

Monoclonal antibodies were conjugated with DTPA (diethylene triaminopentaacetic acid) using the cyclic-anhydride form (Sigma) followed by radiolabelling with 111In (molarity 0.04 M, carrier-free, Amersham Int., UK) as described by Hnatiowich et al. (1983). The labelled antibody
was separated from free $^{111}\text{In}$ using gel filtration (Sephadex G 50). Antibody–DTPA conjugate before and after labelling with indium was assessed for immuno-reactivity by enzyme-linked immunosorbant assay (ELISA) with delipidated milk fat globule protein acting as target for the antibody, fixed on 96-well plastic plates (Epenetos et al., 1986).

**Immunohistology**

After the tissues were counted, they were fixed in formalin, embedded in paraffin and sectioned. The sections were stained by an indirect two-stage immunoperoxidase procedure. The concentration of the antibody was 10 $\mu$g ml$^{-1}$. The sections were scored on the basis of the percentage of cells stained. Positive tissues were scored when 50% or more of the tumour cells were stained.

**Biodistribution studies**

Tumour and normal tissues were removed at operation 24 or 48 h after antibody administration. All the tissues removed at operation were labelled according to the anatomical location, and two representative specimens of each were immediately weighed and counted in a gamma-counter against a standard of the injectate, in order to establish the percentage of injected dose per gram of tissue. Tumour and normal tissue were classified as such only after histological examination. Biopsies from necrotic areas were excluded from the calculation.

**Kinetic studies**

Blood samples were taken at various intervals and urine was collected for 5 days following the administration of the antibody. Aliquots of the plasma and urine were counted in a gamma-counter along with a standard of the injectate for clearance studies. Blood in heparinised tubes was centrifuged and the pellet was washed twice in order to quantitate the radioactivity in the pellet and the supernatant. Protein bound indium in the plasma was quantitated by chromatography (Sephadex G50).

*In vivo* and in vivo stability of the indium-labelled antibodies was assessed by SDS-polyacrylamide gel electrophoresis and autoradiography as described elsewhere (Kalofonos et al., 1988a).

**Imaging studies**

Antibody scans were generated in 15 patients with primary or metastatic breast cancer, using a 40 cm field-of-view gamma-camera with a medium energy collimator. Imaging studies were carried out on at least three points in every patient. Anterior and posterior whole body scans as well as spot views were obtained. The relative percentage of activity in the liver was calculated from the whole body scans by dividing the geometric mean of the counts in the liver by the geometric mean of the counts in the whole body.

**Results**

**Radiolabelling**

Monoclonal antibodies were conjugated with DTPA and radiolabelled with $^{111}\text{In}$ resulting in approximately one molecule of indium being attached onto one molecule of antibody as described by Hnatowich et al. (1983). Labelling efficiencies of 85–90% were achieved. Specific activity was in the range of 3–5 mCi mg$^{-1}$. No significant loss of the immunoreactivity of the F(ab')$\text{2}$ fragments was found in comparison with the intact IgG, and no significant loss was found before and after DTPA coupling and radiolabelling.

**Immunohistology**

HMFG1 F(ab')$\text{2}$ fragments and intact IgG were positive in indirect immunoperoxidase reactions against all breast tissues and $4C4$ F(ab')$\text{2}$ fragments were negative against all breast tissues.

**Biodistribution study**

Table I summarises the biodistribution of indium labelled antibodies in breast cancer patients. The mean tumour uptake with HMFG1 F(ab')$\text{2}$ fragments at 24 h was 5.8 $\times 10^{-3}$% of injected dose per gram of tissue (Figure 1). This was significantly higher than whole IgG, 2.9 $\times 10^{-3}$%IDg$^{-1}$ ($P<0.01$) and non-specific antibody 1.7 $\times 10^{-3}$%IDg$^{-1}$ ($P<0.05$). At 48 h there was no significant difference between F(ab')$\text{2}$ fragments (5.9 $\times 10^{-3}$%IDg$^{-1}$) and intact IgG (6.9 $\times 10^{-3}$%IDg$^{-1}$), but both were higher than the non-specific antibody uptake 1.6 $\times 10^{-3}$%IDg$^{-1}$ ($P<0.05$). Lymph node metastases, interestingly, showed higher antibody uptake than the correspondingly primary tumours (Table I) ($P<0.05$). However, although lymph nodes with tumour infiltration showed higher antibody uptake than normal lymph nodes the difference was not statistically significant.

**Kinetic studies**

Blood clearance was identical for both HMFG1 and $4C4$ F(ab')$\text{2}$ fragments. This was biphasic with a mean half-life of the first component $T_{1/2a}=2.5\pm1.3$ h and of the second component $T_{1/2b}=48\pm4.3$ h. The HMFG1 intact antibody was cleared from the blood more slowly with $T_{1/2a}=24\pm2.8$ h and $T_{1/2b}=58\pm3.8$ h (Figure 2). The cumulative urinary excretion of the indium label over 5 days was 10.6±2.6% and 9.8±2.8% of the injected dose in the patients studied with

Table I Biodistribution of $^{111}\text{In}$ labelled HMFG1 intact and F(ab')$\text{2}$ as well as $4C4$ F(ab')$\text{2}$ fragments in breast cancer patients (% injected dose g$^{-1}$ $\times 10^{-3}$ (mean ± s.d.), at 24 and 48 h after injection)

|                | HMFG1  | HMFG1-F(ab')$\text{2}$ | 4C4-F(ab')$\text{2}$ |
|----------------|--------|------------------------|---------------------|
| 24 h           |        |                        |                     |
| Blood          | 14.0±2.5 | 9.0±2.1               | 8.8±2.2              |
| Tumour         | 2.9±0.5 | 5.8±0.7               | 1.7±0.6              |
| Normal breast  | 1.6±0.4 | 1.8±0.3               | 1.4±0.2              |
| Lymph node (tumour) | 5.8±1.2 | 9.1±1.8               | 4.4±1.3              |
| Lymph node (normal) | 5.3±1.8 | 6.1±1.2               | 4.9±1.4              |
| Fat            | 0.5±0.1 | 0.4±0.2               | 0.4±0.2              |
| Skin           | 1.8±0.3 | 1.4±0.1               | 0.4±0.3              |
| 48 h           |        |                        |                     |
| Blood          | 10.1±1.4 | 6.3±1.0               | 6.0±0.9              |
| Tumour         | 6.9±0.9 | 5.9±0.8               | 1.6±0.6              |
| Normal breast  | 1.7±0.3 | 0.8±0.2               | 0.9±0.3              |
| Lymph node (tumour) | 8.6±1.4 | 8.8±1.7               | –                   |
| Lymph node (normal) | 7.8±1.7 | 7.6±2.1               | –                   |
| Fat            | 0.4±0.1 | 0.5±0.2               | 0.3±0.2              |
| Skin           | 1.7±0.3 | 1.7±0.3               | 0.6±0.3              |

Numbers indicate % injected dose g$^{-1}$ $\times 10^{-3}$ (mean ± s.d.); n, number of patients.
F(ab')₂ fragments and the intact antibody respectively. In all the patients studied, the majority of the radioactivity (95%) was associated with the plasma rather than the blood cells. The mean percentage of the non-protein-bound indium in the serum samples of the patients studied with HMFG1 F(ab')₂ fragments was 3.64 ± 0.86, 2.74 ± 0.64 and 2.68 ± 0.88% and in the patients studied with the HMFG1 intact antibody was 3.57 ± 1.16, 2.62 ± 0.26 and 2.46 ± 1.22% at 10 min, 24 h and 48 h respectively. In vitro and in vivo stability of the radiolabelled antibody was shown to be satisfactory and there was no evidence of significant aggregate formation immediately after radiolabelling, nor in patient serum samples after antibody administration as assessed by SDS-polyacrylamide gel electrophoresis (PAGE) and autoradiography. PAGE showed that most of the radioactivity in the plasma was associated with the monoclonal antibodies.

**Imaging studies**

Table II summarises the imaging results. Among 15 patients with breast cancer investigated with indium-111-labelled HMFG1 F(ab')₂ fragments by external body scintigraphy, we observed successful localisation in three out of seven patients with primary breast cancer (Figure 3), in four out of six patients with bone metastases, in two out of four with skin metastases, in one out of two with lymph node infiltration and in one out of two with liver metastases. The gamma-camera images showed considerable uptake of radioactivity by liver. There was also significant uptake by spleen and kidneys. The relative fraction of the injected radioactivity in the liver over 4 days remained constant, which was estimated to be approximately 20% of the administered dose.

**Discussion**

This study shows that the amount of ¹¹¹In-labelled F(ab')₂ fragments and intact HMFG1 monoclonal antibody reaching target tissues after i.v. administration is relatively small. However, it clearly demonstrates the ability of this antibody to bind specifically to breast cancer lesions resulting in successful immunolocalisation of approximately 50% of cancer lesions.

One objective of this study was to assess the localising effectiveness of ¹¹¹In-labelled HMFG1 F(ab')₂ fragments for imaging in patients presenting with measurable disease, and to compare this with the distribution of the disease as determined by conventional methods. The results of our studies show high specificity but low overall sensitivity. We have shown no false positive localisation in 15 patients studied. However, this technique suffers from an inability to detect all known tumour sites. Epenetos et al. (1982), using ¹²⁵I-labelled intact HMFG1 and HMFG2 monoclonal antibodies, studied six breast cancer patients. They observed successful immunolocalisation in most of primary and metastatic lesions but the number of patients studied with each antibody was small. Rainsbury (1984), working with another antibody (LCR-LON-M8), also directed against a component of human milk fat globule and radiolabelled with ¹¹¹In, demonstrated successful localisation in breast cancer patients with bone metastases, but not in primary tumours and the soft tissue metastases. In this current study we have demonstrated successful localisation in primary tumours, skeletal metastases and soft tissue metastases. This could be explained by the faster clearance of blood pool radioactivity along with the easier tumour accretion after administration of the F(ab')₂ fragments. These findings favour the use of F(ab')₂ fragments for tumour radioimmunolocalisation and are in agreement with our previous experience (Kalofonos et al., 1984a) and the experience of others (Wahl et al., 1983; Buraggi et al., 1985; Munz et al., 1986; Chatel et al., 1987). Bone metastases were detected in a higher percentage (67%) than the primary tumour (43%) or metastases in other organs (50%) possibly due to the easier access of the antibody to bone metastases through the rich medullary blood supply.

In this study we observed significant non-specific concentration of the ¹¹¹In in the liver, the spleen and the kidneys. The accumulation of ¹¹¹In in the kidneys with the F(ab')₂ fragments may be due to antibody catabolism (Covell et al., 1986), active filtration (Khaw et al., 1984) and exchange of ¹¹¹In into ion-binding proteins within this organ. Accumulation of ¹¹¹In by the liver is not well understood and could be a result of antibody catabolism and exchange with iron-binding protein (Sands & Jones, 1987).

Most of the previous clinical trials using radiolabelled monoclonal antibodies have relied solely on scans to determine the accuracy of tumour binding by the monoclonal antibody. In only a few trials have actual tumour biopsy material been obtained for direct analysis of monoclonal antibody delivery (Epenetos et al., 1986; Esteban et al., 1987; Ward et al., 1987). In this study it became

![Figure 2](image2.png)

**Figure 2** Half-life of the radiolabelled HMFG1 intact IgG and F(ab')₂ fragments in the blood.

| Table II | Antibody guided tumour detection with HMFG1-F(ab')₂ fragments |
|----------|---------------------------------------------------------------|
| **Tumour** | **Patients** | **Positive** | **Negative** |
| Primary breast cancer | 7 | 3 | 4 |
| Lymph node metastases | 2 | 1 | 1 |
| Bone metastases | 6 | 4 | 2 |
| Skin metastases | 4 | 2 | 2 |
| Liver metastases | 2 | 1 | 1 |
obvious that antibody localisation to the target was relatively small. However, we observed significantly higher specific antibody uptake than the irrelevant antibody by primary breast tumours. There are different factors which could account for the low accessibility of monoclonal antibodies in the tumours including the lack of vascularity as well as the amount and the type of the interstitial stroma (Sandis et al., 1988; Jain, 1987). Breast cancer has a dense stromal component which may inhibit the accessibility of the antibody to reach all the antigen expressing tumour cells in different areas of the tumour. Another important observation in this study was that the F(ab')2 fragments accumulated in the tumour faster, with maximum uptake being achieved as early as 24 h, compared to the intact antibody where it was gradually increased and equivalent uptake achieved at 48 h. F(ab')2 fragments with molecular weight lower than intact IgG and comparable immunoreactivity are cleared faster from the vascular moving to the extravascular compartment, resulting in an increase in tumour to background ratio.

In conclusion, this study demonstrates that 111In-labelled HMFG1 F(ab')2 fragments can specifically localise breast cancer lesions, but results obtained so far are inferior to conventional radiology such as isotope bone scanning. F(ab')2 fragments localise faster in the tumour than the intact antibody and are cleared faster from the blood pool, favouring their use for in vivo tumour localisation. However, this study also illustrates the relatively low antibody uptake of both IgG and F(ab')2 fragments by breast cancer. This method needs further improvement before becoming useful in clinical practice.

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