Breast Cancer Res Treat (2010) 124:745–753
DOI 10.1007/s10549-008-0131-1

EPIDEMIOLOGY

# Prevalence of renal insufficiency in breast cancer patients and related pharmacological issues

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Received: 26 May 2008 / Accepted: 8 July 2008 / Published online: 15 August 2008


**Abstract** The Renal Insufficiency and Anticancer Medications (IRMA) study is a French national, observational study which demonstrated the high prevalence of abnormal renal function in a population of 4,684 solid tumour patients. Among them, 50–60% had decreased renal function defined as CrCl below 90 and 80% were treated with anticancer drugs that either necessitated dosage adjustment in case of RI or were potentially nephrotoxic drugs. Since patients and drugs used differ depending on the type of tumour, the IRMA Study Group started analyses in different subgroups of patients. In the 1898 IRMA patients with breast cancer, the prevalence of RI was still very high in spite of a normal serum creatinine in almost all cases. Some anticancer drugs, as in particular some bisphosphonates, capecitabine and platinum salts, may be nephrotoxic and/or need dosage adjustment. However other important drugs in breast cancer do not require dose reduction, and do not present with potential nephrotoxicity (anthracyclines, taxanes, trastuzumab). Both issues seem to be slightly but significantly more important in patients with bone metastases as compared to patients with a non-metastatic disease.

**Keywords** Breast Cancer · Renal insufficiency · Drug dosage adjustment · Nephrotoxicity · Kidney disease

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## Introduction

The increased incidence of malignancies in patients with chronic renal failure has been discussed since the mid-1970s [1, 2]. In their study, Cengiz et al. [3] reported that 188 (6.7%) organ tumors of varying pathologies were found in 2,817 patients with chronic renal failure. Although it is known to be a common pathology in the general population [4], the prevalence of renal insufficiency (RI) among patients with cancer has only been recently assessed in the "renal insufficiency and anticancer medications" (IRMA) study [5], where we found a high prevalence of renal insufficiency among 4,684 solid tumor patients from 15 French cancer centers. Only 7.2% had elevated serum creatinine (SCR) but 50–60% had creatinine clearance (CrCl) below 90 ml/min, with the majority of them between 60 and 90, which defines a stage 2 kidney disease according to the K/DOQI-KDIGO official international definition [6, 7]. Such a reduction in

renal function may be too low to be of significant clinical importance in the oncology setting. This should however be considered, especially for patients near 60, as a risk factor for developing more severe renal insufficiency. Furthermore, markers of renal damage, which are part of the criteria required to define a stage 2 renal disease, were not recorded in the IRMA study. When present, i.e. when a stage 2 kidney disease is actually diagnosed, nephrological investigations may be needed. This high prevalence of RI is an important issue in clinical practice for the handling of anticancer drugs in those patients. Since some anticancer drugs used in breast cancer are excreted predominantly in the urine as unchanged drug or active metabolite(s), any reduction in renal clearance results in accumulation of potentially toxic species and overdosage. The dosage of chemotherapeutic agents used in these patients with RI will, therefore, require dosage reduction to avoid severe toxicities. Furthermore, using potentially nephrotoxic anticancer drugs will also require specific monitoring and, when available, specific prevention methods in order to help reduce the risk for renal toxicity, especially in patients with baseline abnormal renal function before anticancer therapy is started.

The development of platinum-based chemotherapy for triple-negative [8] and HER2 positive [9–12] breast cancers, in particular the emerging and promising strategies associating a taxane, a platinum salt and trastuzumab, and the growing use of IV bisphosphonates (BP) emphazise the need for regular monitoring of renal function, with particular attention to patients with preexisting impaired renal function.

In breast cancer patients with bone metastases (BM), there is a paucity of data for optimal use of BP mainly regarding initiation and treatment duration. Benefit with zoledronate and ibandronate has been shown for a treatment duration of up to 2 years [13, 14]. Renal safety must be considered because over the past few years, case reports and randomized trials [15] have raised cases of renal toxicity with IV BP, for instance with zoledronic acid-associated renal impairment leading to renal failure [16].

Monitoring must include an appropriate evaluation of CrCl in patients receiving IV BP because SCR values can be misleading.

Here are presented the results from the subgroup analysis of the 1,898 Breast Cancer (BC) patients in the IRMA population.

## Methods

### Study design for the IRMA study

The IRMA study included a total of 4,684 patients being treated for solid tumors (either in hospital or as outpatients) in an oncology department. The study consisted of a retrospective patient data collection on one of two, specific, 15-day time periods between either the 1st and the 15th of February 2004 or the 1st and the 15th of October 2004. These time periods were selected to avoid summer vacations and to be representative of the whole year, with one period in winter/spring and the other in fall/winter. Patients were included regardless of disease pathology, treatment (antineoplastic drugs used/to be used, pretreated or not). Patients were excluded if they were <18 years of age, had a diagnosis of myeloma, or presented with end-stage renal disease requiring renal replacement therapy (either hemodialysis or peritoneal dialysis) since the aim of the IRMA study was to determine the prevalence of potentially undiagnosed RI, meaning non-dialysis patients, those latter obviously presenting with this disease.

The following data were collected for each patient: sex, age, weight, serum creatinine, blood urea nitrogen, hemoglobinemia, type of tumor, metastasis, and anticancer drugs prescribed. Patients who were known to present with acute renal failure were excluded in order to determine the prevalence of potentially chronic abnormal renal function. Estimations of renal function were made by calculation from SCR using the Cockcroft–Gault (CG) formula [17] and the abbreviated Modification of Diet in Renal Disease (aMDRD) formula [18].

Cockcroft–Gault formula:

$$\mathrm{CrCl(ml/min)} = k \times [(140 - \mathrm{age}) \times \mathrm{weight(kg)}]/\mathrm{SCR}(\mu\mathrm{mol/l})$$

$k = 1.23$ (male) or 1.04 (female); CrCl = creatinine clearance;
SCR = serum creatinine.

aMDRD formula:

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73\ m^2}\right) = k \times 186 \times [\mathrm{SCR}]^{-1.154} \times [\mathrm{age}]^{-0.203}$$

$k = 1$ (male) or 0.742 (female); GFR = glomerular filtration rate;
SCR = serum creatinine (mg/dl).

Renal function, calculated using either formula, was staged in accordance with the international clinical practice guidelines from the K/DOQI and the KDIGO [6, 7]:

- Stage 1: GFR $\geq$ 90 ml/min
- Stage 2: GFR 60–89 ml/min
- Stage 3: GFR 30–59 ml/min
- Stage 4: GFR 15–29 ml/min
- Stage 5: GFR < 15 ml/min

With regard to anticancer therapies prescribed to study patients, those requiring dosage adjustment were identified in accordance with their pharmacokinetics and available

recommendations from both their individual Summary of Product Characteristics (SmPC), and from two specific reference books on drug dosage adjustment in patients with RI: Drug prescribing in renal failure. Dosing guidelines for adults, 4th edition [19] and GPR Anticancéreux. Guide de prescription des médicaments chez le patient insuffisant rénal. 3ème édition [20]. Anticancer therapies were then classified as "Yes" when adjustment was required, "No" when adjustment was not necessary, and "ND" when no data were available in the literature. To obtain profiles of anticancer therapies with regard to renal tolerance, an exhaustive literature search was performed using PubMed to identify any potential renal side effects of the therapies. If, at least, some cases of nephrotoxicity were retrieved, the therapy was classified as "Yes", meaning "potentially nephrotoxic." Therapies were labeled "No" when no cases had been found or there were no suggestions of potential renal toxicity. As a result, some drugs with different risks for renal toxicity may be similarly classified as "Yes". For instance, Tamoxifen and Paclitaxel are both reported as potentially nephrotoxic because those drugs have been reported with one case of nephrotic syndrome for Tamoxifen [21], and evidence of increased renal toxicity of Cisplatin + Paclitaxel versus Cisplatin alone [22], respectively.

## Results of the breast cancer subgroup analysis

### Patient demographics

A total of 1,898 patients with breast cancer were included in the study. Of these, 20 patients were men, and the mean age of all patients was 55.1 years (range 23–95). Nearly one-third of the patients (30.4%) had BM.

### Renal insufficiency

Table 1 shows the percentages of patients among the five stages of RI. In Fig. 1 are presented the number of patients in each stage according to the formula used to estimate renal function, either CG or aMDRD.

For 10.5% of patients, no SCr could be retrieved in the medical file, and among the whole population of breast cancer patients, only 31 (1.63%) had a SCR level ≥110 µmol/l. In spite of this low proportion of patients with elevated SCR, a majority of patients had in fact a decreased CrCl or eGFR: 51.8 and 50.8% of patients had abnormal renal function (<90 ml/min) when calculated using the CG or aMDRD formulae, respectively (Table 1). This high prevalence of RI was also observed in the 1,667 patients (87.8%) whose SCR levels were normal, i.e. <110 µmol/l: 57.1 and 56.0% of those patients had abnormal renal function (<90 ml/min) when calculated using the CG or aMDRD formulae, respectively.

**Table 1** Renal function of the 1898 IRMA patients with breast cancer using the Cockcroft–Gault and the Amdrd formulae

| | Cockcroft & Gault CrCl (ml/min) | | aMDRD eGFR (ml/min/1.73 $m^2$) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| ≥90 | 697 | 36.7 | 733 | 38.6 |
| 89–60 | 713 | 37.6 | 817 | 43.0 |
| 59–30 | 261 | 13.7 | 141 | 7.4 |
| 29–15 | 7 | 0.4 | 5 | 0.3 |
| <15 | 2 | 0.1 | 2 | 0.1 |
| ND | 218 | 11.5 | 200 | 10.6 |
| | | 100 | | 100 |

CrCl, Creatinine clearance; eGFR, estimated glomerular filtration rate; *N*, Number of patients

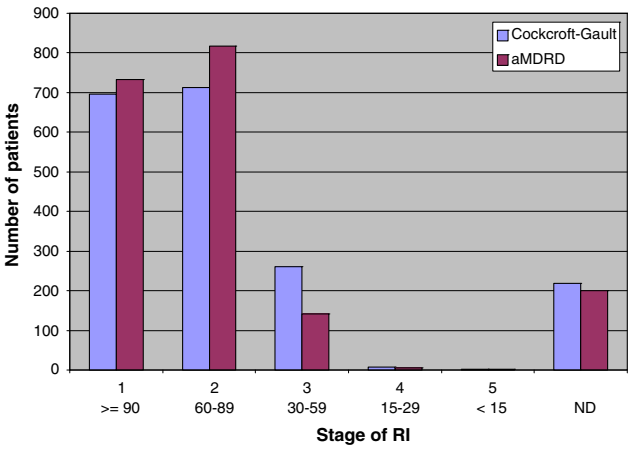


**Fig. 1** Comparison of screening breast cancer patients for renal insufficiency with Cockcroft–Gault or Amdrd

The prevalence of RI in IRMA breast cancer patients was also studied in patients with BM as compared to patients without BM. Table 2 describes the two populations of patients: patients with breast cancer and BM and patients with breast cancer without BM. Serum creatinine was elevated (≥110 µmol/l) in only 2.8% of patients with BM and in 1.1% of patients without BM ($P = 0.0036$). Patients with BM were significantly older (57.7 vs. 53.9 years, $P < 0.0001$) and had a higher (but not significantly, $P = 0.06$) mean SCR (70.4 vs. 68.0 µmol/l). Mean CG estimates of renal function differed between groups (84.1 vs. 89.7 ml/min, $P = 0.0004$). However, they were not statistically different when estimating renal function with aMDRD (88.1 vs. 89.2, $P > 0.05$) Table 3.

However, when calculating the prevalence of RI in those two groups of patients (Table 4), some significant differences appeared. The prevalence of renal dysfunction was as follows:

**Table 2** Characteristics of breast cancer patients in the IRMA study with or without bone metastases

| | Patients with BM ($N = 577$) | | Patients without BM ($N = 1321$) | | *P*-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 57.7* | 11.2 | 53.9* | 11.4 | <0.0001 |
| Weight (kg) | 63.6 | 13.5 | 64.5 | 13.3 | >0.05 |
| SCR (μmol/l) | 70.4 | 27.2 | 68.0 | 15.4 | >0.05 |
| CG (ml/min) | 84.1* | 30.8 | 89.7* | 29.5 | 0.0004 |
| aMDRD (ml/min/1.73 $m^2$) | 88.1 | 27.7 | 89.2 | 23.3 | >0.05 |
| Hb (g/dl) | 11.7* | 1.5 | 12.1* | 1.3 | <0.0001 |

BM, Bone metastases; SCR, serum creatinine; CG, Cockcroft–Gault formula; aMDRD, abbreviated modification of diet in renal disease formula; Hb, hemoglobinemia

* Indicates values that are statistically different

**Table 3** Renal function of IRMA breast cancer patients with or without bone metastases

| | Breast cancer patients with BM ($N = 577$) | | Breast cancer patients without BM ($N = 1321$) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Cockcroft–Gault CrCl (ml/min) | | | | |
| ≥90 | 198 | 34.3 | 499 | 37.8 |
| 89–60 | 209 | 36.2 | 504 | 38.2 |
| 59–30 | 112 | 19.4 | 149 | 11.3 |
| 29–15 | 3 | 0.5 | 4 | 0.3 |
| <15 | 2 | 0.4 | 0 | 0 |
| ND | 53 | 9.2 | 165 | 12.5 |
| aMDRD GFR (ml/min/1.73 $m^2$) | | | | |
| ≥90 | 212 | 36.7 | 521 | 39.4 |
| 89–60 | 260 | 45.1 | 557 | 42.2 |
| 59–30 | 53 | 9.2 | 88 | 6.7 |
| 29–15 | 3 | 0.5 | 2 | 0.2 |
| <15 | 2 | 0.4 | 0 | 0.0 |
| ND | 47 | 8.2 | 153 | 11.6 |

BM, Bone metastases; *N*, number of patients; CrCl, creatinine clearance; GFR, glomerular filtration rate

62.2% of breast cancer patients with BM had a CG creatinine clearance below 90 ml/min as compared to 56.8% of patients without BM ($P = 0.0381$) and 60.0% of breast cancer patients with BM had an aMDRD estimated glomerular filtration rate below 90 ml/min/1.73 $m^2$ versus 55.4% in patients without BM ($P > 0.05$). There was thus a statistically significant difference in the prevalence of renal insufficiency with CG but the difference was not significant with aMDRD.

Anemia, according to the WHO definition (<12 g/dl in women and <13 g/dl in men) was observed in 44.1% of IRMA breast cancer patients. Further analysis showed that 2.1 and 18.4% of the patients had a hemoglobin level lower than 9 g/dl and within 9–11 g/dl, respectively. For 5.1%, no hemoglobin value was available in the medical file of the patient. Comparing patients with or without BM and for whom a hemoglobin value was available (Table 5), it appeared that patients with BM had statistically significantly more often hemoglobin levels within 9 and 11 and lower than 9 as compared to patients without BM: 25.1 vs. 15.5% and 3.6 vs. 1.4%, respectively.

## Anticancer drugs

Among the whole study population of 1,898 breast cancer patients, 89.7% were receiving anticancer drugs during the tie period studied. This resulted in 1,702 treated patients for a total number of anticancer drugs prescriptions of 3,465, i.e. 2.0 drugs/patient.

The prescriptions comprised 40 different drugs (Table 6) of which 35% are drugs that necessitate dosage adjustment in RI and 30% are drugs for which no data were available in the literature on whether it would be necessary or not to adjust their dosage in case of renal impairment. Of the 3,465 prescriptions, 53.2% were for drugs for which a dosage adjustment was necessary, or for which there were no available data concerning administration in patients with RI, 44.8 and 8.4%, respectively. Finally, 80.2% of the patients were receiving at least one drug that necessitates

**Table 4** Comparison of the prevalence of RI in breast cancer patients with or without bone metastases, for patients with available data

| Renal function | Patients with BM ($N = 524$) | Patients without BM ($N = 1156$) | *P*-value |
|---|---|---|---|
| CG < 90 | 62.2% | 56.8% | 0.0381 |
| CG ≥ 90 | 37.8% | 43.2% | |
| | ($N = 530$) | ($N = 1,168$) | |
| aMDRD < 90 | 60.0% | 55.4% | 0.05 |
| aMDRD ≥ 90 | 40.0% | 44.6.% | |

BM, Bone metastases; CG, Cockcroft–Gault formula (ml/min); aMDRD, abbreviated modification of diet in renal disease formula (ml/min/1.73 $m^2$)

**Table 5** Hemoglobin values in IRMA breast cancer patients with or without bone metastases, for patients with available

| Hb value | Patients with BM ($N = 539$) | Patients without BM ($N = 1262$) |
|---|---|---|
| ≥11 | 69.2% | 82.3% |
| 9–11 | 26.9% | 16.2% |
| <9 | 3.9% | 1.5% |

Hb, Hemoglobin (g/dl); BM, bone metastases

**Table 6** Anticancer drugs prescribed to breast cancer patients in the IRMA study (1,702 treated patients—3,465 prescriptions)

| INN | Number of prescriptions | Percentage of the total number of prescriptions | Need for dosage adjustment | Potential nephrotoxicity |
|---|---|---|---|---|
| Cyclophosphamide | 631 | 18.21 | Yes | No |
| 5-FU | 618 | 17.84 | No | No |
| Epirubicin | 544 | 15.70 | No | Yes (isolated cases) |
| Docetaxel | 379 | 10.94 | Yes | No |
| Vinorelbine | 271 | 7.82 | Yes | No |
| Trastuzumab | 251 | 7.24 | ND | Yes (isolated cases) |
| Doxorubicin | 175 | 5.05 | No | Yes (isolated cases) |
| Paclitaxel | 125 | 3.61 | No | Yes (isolated cases) |
| Zoledronate | 112 | 3.23 | Yes | Yes |
| Gemcitabine | 79 | 2.28 | No | Yes |
| Capecitabine | 60 | 1.73 | Yes | No |
| Methotrexate | 40 | 1.15 | Yes | Yes |
| Carboplatin | 28 | 0.81 | Yes | Yes |
| Mitomycin C | 19 | 0.55 | Yes | Yes |
| Oxaliplatin | 13 | 0.38 | No | Yes |
| Tamoxifen | 12 | 0.35 | No | Yes (isolated cases) |
| Vindesine | 12 | 0.35 | No | No |
| Pirarubicin | 11 | 0.32 | ND | Yes (isolated cases) |
| Letrozole | 9 | 0.26 | No | No |
| Vinblastine | 9 | 0.26 | No | No |
| Anastrozole | 8 | 0.23 | No | No |
| Cisplatin | 8 | 0.23 | Yes | Yes |
| Mitoxantrone | 8 | 0.23 | No | No |
| Pamidronate | 7 | 0.20 | ND | Yes |
| Exemestane | 6 | 0.17 | No | No |
| Thiotepa | 6 | 0.17 | ND | Yes |
| Irinotecan | 4 | 0.12 | ND | Yes |
| Goserelin | 4 | 0.12 | ND | No |

Anticancer drugs prescribed less than 0.1% in IRMA breast cancer patients were (decreasing number of prescriptions): DHER vaccine, Fotemustin, Temozolomide, Etoposide, Ixabepilone, Clodronate, Edotecarine, Estramustine, Interferon, Interleukin-2, Melphalan, and Megestrol. INN, International non-proprietary name; 5-FU, 5-fluorouracile

dosage adjustment in RI and 10.2% at least one drug for which no data were available, resulting in a total 90.4% of breast cancer patients in IRMA with at least one drug for which caution is mandatory in RI (either dosage adjustment required or no data available). Regarding nephrotoxicity, 65% of the drugs were potentially toxic to the kidneys (57.5%) or for which there were no data in the literature on their renal tolerance (7.5%). Among the prescriptions, 41.7% were prescriptions of drugs that may be nephrotoxic, and 76.9% of breast cancer patients in IRMA were receiving at least one drug that may exhibit renal toxicity.

## Discussion

In this study we found that RI is highly prevalent in breast cancer patients. However, the frequency of RI clearly is routinely underestimated in clinical practice because physicians most often base their diagnosis on SCR measurements. It is crucial to outline that SCR is not appropriate for evaluating renal function. We observed that 10.5% of our patients had no report of SCr determination in their file. Even if those patients with no available SCr may be those who were only seen for a routine control and/or patients who were not treated or treated with non-nephrotoxic drugs (such as trastuzumab), it remains important to (1) measure SCr on a regular basis, the frequency being determined according to the patient's renal function, and (2) to report it in the patient's file.

It is furthermore of major importance that renal function is appropriately evaluated in all breast cancer patients by estimating CrCl or GFR calculated using either the CG or aMDRD formulae. This includes patients who have normal SCR levels since even in those with a so-called "normal" serum creatinine level, the frequency of stage 2 or more RI was 57.1 and 56.0% with CG or aMDRD formulae, respectively.

To date there are no data allowing recommending the use of one formula over the other, in oncology patients as

**Table 7** Anticancer drugs prescribed to breast cancer patients with bone metastases in the IRMA study (529 treated patients—912 prescriptions)

| INN | Number of prescriptions | Percentage of the total number of prescriptions | Need for dosage adjustment | Potential nephrotoxicity |
|---|---|---|---|---|
| Docetaxel | 125 | 13.7 | Yes | No |
| Vinorelbine | 121 | 13.3 | Yes | No |
| Zoledronate | 107 | 11.7 | Yes | Yes |
| Trastuzumab | 87 | 9.5 | ND | Yes (isolated cases) |
| 5-FU | 78 | 8.6 | No | No |
| Paclitaxel | 62 | 6.8 | No | Yes (isolated cases) |
| Cyclophosphamide | 57 | 6.3 | Yes | No |
| Epirubicin | 47 | 5.2 | No | Yes (isolated cases) |
| Gemcitabine | 40 | 4.4 | No | Yes |
| Doxorubicin | 35 | 3.8 | No | Yes (isolated cases) |
| Capecitabine | 34 | 3.7 | Yes | No |
| Methotrexate | 19 | 2.1 | Yes | Yes |
| Carboplatin | 16 | 1.8 | Yes | Yes |
| Mitomycin C | 12 | 1.3 | Yes | Yes |
| Oxaliplatin | 7 | 0.8 | No | Yes |
| Letrozole | 6 | 0.7 | No | No |
| Pamidronate | 6 | 0.7 | ND | Yes |
| Vindesine | 6 | 0.7 | No | No |
| Cisplatin | 5 | 0.5 | Yes | Yes |
| Thiotepa | 5 | 0.5 | ND | Yes |
| Vinblastine | 5 | 0.5 | No | No |
| Irinotecan | 4 | 0.4 | ND | Yes |
| Mitoxantrone | 4 | 0.4 | No | No |
| Exemestane | 4 | 0.4 | No | No |
| Pirarubicin | 4 | 0.4 | ND | Yes (isolated cases) |
| Anastrozole | 3 | 0.3 | No | No |
| Tamoxifen | 3 | 0.3 | No | Yes (isolated cases) |
| Goserelin | 3 | 0.3 | ND | No |
| Etoposide | 2 | 0.2 | Yes | No |

Anticancer drugs prescribed less than 0.1% in IRMA breast cancer patients with bone metastases were (decreasing number of prescriptions): Clodronate, Edotecarine, Melphalan, Megestrol, Temozolomide. INN, International non-proprietary name; 5-FU, 5-fluorouracile

well as in the general population. Most often, differences between the two formulae in terms of renal function are weak. Some differences may be observed in the ranging of the patients in the different stages of RI. As shown on Fig. 1, such differences between the two formulae were not relevant in our patients. However, when the CG and the aMDRD estimates differ in a particular patient, it may be useful to consider a measure of the actual GFR, after discussions with a nephrologist. Such methods include a 24-h urine collection to measure creatinine clearance or a measure of the actual GFR using a specific marker of renal filtration such as $^{51}$CR-EDTA, for instance. However, such methods necessitate a trained staff, time, and are not cost-effective for a systematic evaluation of patients' renal function. They must be used only in some specific cases, and patients who may benefit from such a determination of renal function should be closely identified together with nephrologists, according to the patient's profile and its estimated renal function with CG and aMDRD.

In patients with stage 2 RI, potential drug-nephrotoxicity is the main issue. Many studies have demonstrated that pre-existing abnormal renal function is a risk factor for drug-induced nephrotoxicity [23]. As a result, in those patients with mildly decreased renal function, anticancer drugs, antineoplastic or supportive care, should be cautiously selected in order to administer drugs that are not or are less nephrotoxic.

When renal function is lower than 60 ml/min, the risk for nephrotoxicity is even higher, and moreover, the clinical consequences are more severe since any further deterioration of renal function may precipitate end-stage renal disease. In those patients, in addition to nephrotoxicity, the question of drug dosage adjustment is crucial to avoid overdose due to accumulation of the drug from reduced excretion and related toxicities, such as neurological,

**Table 8** Anticancer drugs prescribed to breast cancer patients without bone metastases in the IRMA study (1,173 treated patients—2,553 prescriptions)

| INN | Number of prescriptions | Percentage of the total number of prescriptions | Need for dosage adjustment | Potential nephrotoxicity |
|---|---|---|---|---|
| Cyclophosphamide | 574 | 22.48 | Yes | No |
| 5-FU | 540 | 21.15 | No | No |
| Epirubicin | 497 | 19.47 | No | Yes (isolated cases) |
| Docetaxel | 254 | 9.95 | Yes | No |
| Trastuzumab | 164 | 6.42 | ND | Yes (isolated cases) |
| Vinorelbine | 150 | 5.88 | Yes | No |
| Doxorubicin | 140 | 5.48 | No | Yes (isolated cases) |
| Paclitaxel | 63 | 2.47 | No | Yes (isolated cases) |
| Gemcitabine | 39 | 1.53 | No | Yes |
| Capecitabine | 26 | 1.02 | Yes | No |
| Methotrexate | 21 | 0.82 | Yes | Yes |
| Carboplatin | 12 | 0.47 | Yes | Yes |
| Tamoxifen | 9 | 0.35 | No | Yes (isolated cases) |
| Mitomycin C | 7 | 0.27 | Yes | Yes |
| Pirarubicin | 7 | 0.27 | ND | Yes (isolated cases) |
| Oxaliplatin | 6 | 0.24 | No | Yes |
| Vindesine | 6 | 0.24 | No | No |
| Anastrozole | 5 | 0.20 | No | No |
| Zoledronate | 5 | 0.20 | Yes | Yes |
| Mitoxantrone | 4 | 0.16 | No | No |
| Vinblastine | 4 | 0.16 | No | No |
| Cisplatin | 3 | 0.12 | Yes | Yes |
| Letrozole | 3 | 0.12 | No | No |

Anticancer drugs prescribed less than 0.1% in IRMA breast cancer patients without Bone Metastases were (decreasing number of prescriptions): DHER vaccine, Fotemustin, Ixabepilone, Estramustin, Interferon, Interleukin-2, Pamidronate, Temozolomide, Thiotepa, Goserelin. INN, International non-proprietary name; 5-FU, 5-fluorouracile

hematological, skeletal, cardiological, and hepatological toxicities. Indeed, when renal function declines and is lower than 60 ml/min, pharmacokinetic changes often necessitate modification of the drug dosage to ensure efficacy and safety.

Over 90% of breast cancer patients in the IRMA population received at least one drug that requires dosage adjustment in patients with RI, or for which there were no data available regarding their use in patients with RI (in either the literature or the SmPC), in spite of the fact that the most important drugs in breast cancer do not require dose reduction, and do not present with potential nephrotoxicity (anthracyclines, taxanes, trastuzumab). In patients who are receiving drugs that require dosage adjustment, renal function should be calculated (with CG or aMDRD formulae) to prescribe drugs at their adjusted dosage in accordance with their renal function, preferably prior to each course of anticancer therapy, chemotherapy or other type of treatment. Where information is not available on dosage adjustments in patients with RI, the prescription of these drugs should be approved by a pharmacologist or a nephrologist, together with the oncologist in charge of the patient. When an alternative treatment exists for which recommendations are available, this should be preferably used.

The use of potentially nephrotoxic therapies in patients at high risk for drug renal toxicity due to pre-existing renal impairment should be avoided if possible and alternative treatments should be considered. However, in IRMA breast cancer patients the frequency of nephrotoxic drug prescriptions was high with 76.85% of the treated patients receiving at least one such drug.

There were significantly ($P < 0.05$) more prescriptions of anticancer drugs necessitating dosage adjustment in RI or drugs being potentially nephrotoxic in breast cancer patients with BM as compared to breast cancer patients without BM (Tables 7–9). However, the percentage of patients receiving at least one such drug was higher in patients without BM, 82.9 vs. 74.5% of treated patients in each group ($P < 0.05$). Furthermore, 78.7% of treated patients without BM received at least one potentially nephrotoxic drug versus 72.2% of patients with BM ($P < 0.05$). This means that patients with BM receive more frequently several drugs that may necessitate dosage adjustment and/or which can be nephrotoxic.

The IRMA study did not allow to evaluate whether the prescription of such drugs was or may have been responsible for the higher frequency of decreased renal function in those breast cancer patients with BM when renal

**Table 9** Comparison of the prescription pattern of drugs that necessitate dosage adjustment in RI or may be nephrotoxic in breast cancer patients with or without bone metastases

| Prescriptions | Patients with BM $N = 912$ | Patients without BM $N = 2,553$ | *P*-values |
|---|---|---|---|
| *Dosage adjustment in RI* | | | |
| Yes | 54.82% | 41.28% | |
| ND | 12.28% | 7.01% | |
| Yes or ND | 67.10% | 48.29% | <0.0001 |
| No | 32.89% | 51.70% | |
| *Nephrotoxicity* | | | |
| Yes | 50.66% | 38.39% | |
| ND | 0.11% | 0.07% | |
| Yes or ND | 50.77% | 38.46% | <0.0001 |
| No | 49.23% | 61.54% | |
| Patients (treated) | $N = 529$ | $N = 1173$ | |
| *Dosage adjustment in RI* | | | |
| Yes | 74.48% | 82.86% | |
| ND | 10.96% | 9.80% | |
| Yes or ND | 85.44% | 92.66% | <0.0001 |
| No | 14.56% | 7.33% | |
| *Nephrotoxicity* | | | |
| Yes | 72.20% | 78.69% | |
| ND | 0.20% | 0.17% | |
| Yes or ND | 72.4% | 78.86% | 0.0035 |
| No | 27.6% | 21.14% | |

BM, Bone metastases; RI, renal insufficiency; ND, no data

function is calculated with aMDRD. For instance, the frequent administration of contrast media for CT scan, which is known to be a potential cause of renal dysfunction, may be one of the etiologies, in addition to or rather than chemotherapy. However, the message that came out was that, once patients are diagnosed with decreased renal function, drug therapy should be re-evaluated, dosages adjusted where necessary, and some potentially nephrotoxic drugs changed for less or non-nephrotoxic ones, when efficacy has been proven to be of a similar range.

In breast cancer therapy, the choice of the anticancer drug to use obeys multiple rules and criteria, indications and protocols. It may not be always possible not to use potentially nephrotoxic drugs. However, it remains very important to be aware of the renal function of patients who receive such drugs and to monitor renal function on a regular basis, prior to each course of therapy during treatment. Depending on the level of renal function of the patient once in remission, a twice-a-year monitoring may be sufficient during follow-up. Furthermore, in those patients who require a nephrotoxic antineoplastic chemotherapy, and especially those with baseline decreased renal function, cautious selection and analysis of associated drugs should be performed. For example, non-steroidal anti-inflammatory drugs, where possible, should be avoided since they may potentate the renal toxicity of chemotherapy.

Regarding the treatment of BM, when a bisphosphonate is to be prescribed, the same selection rules should be applied according to renal tolerance and dosage adjustment. There are no specific limitations for the use of BP in the elderly. Task forces from the International Society of Geriatric Oncology recommended a monitoring of CrCl in every patient, preferably before each course, the use of an agent with the best possible renal tolerability, and the assessment of hydration status [24–26].

In patients with evidence of renal deterioration during treatment, IV BP should be withheld and only resumed when serum creatinine returns to within 10% baseline [27]. In case of mild to moderate renal impairment (CrCl: 30–60 ml/min) regulations recommend lower doses of zoledronate and longer infusion for pamidronate. Treatment with zoledronate is contraindicated in patients with severe dysfunction (CrCl < 30 ml/min).

A recent label of ibandronate approved by European regulatory authorities allows a dosing regimen of 6 mg over 60 min instead of 15 min when CrCl is 30–50 ml/min. Furthermore, a dose reduction for patients whose CrCl is below 30 has been recommended for ibandronate (2 mg instead of 6 mg).

As a result, where available, ibandronate should be preferred to any other IV bisphosphonate since it appears to be nonnephrotoxic and only necessitates dosage adjustment in patients with a CrCl or a eGFR lower than 30 [15, 28]. Oral bisphosphonates may be an option of choice since they are renally well-tolerated.

**Acknowledgements** Under the direction of the IRMA Scientific Committee, the IRMA Study has been coordinated by ICAR, a National Medical Advisory Service on the interactions between drugs and the kidney (i.e. drug dosage adjustment, drug nephrotoxicity, drug–drug interactions with immunosuppressive therapies) located in the Department of Nephrology at Pitié-Salpêtrière Hospital in Paris, France. The authors are indebted to the physicians who took time from their busy work schedules to participate in the IRMA Study Group and to Roche France, thanks to whom ICAR services are available to French oncologists through an unrestricted educational grant.

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