Value of CA 15-3 determination in the initial management of breast cancer patients

CA 15-3 is the most frequently used tumour marker in invasive breast cancer. Despite poor prognosis associated with an initially high value, scientific societies have not yet recommended its determination in the initial evaluation as regards the extent of disease [1–6]. Nevertheless, some institutions, such as the Henri-Becquerel Center (HBC), routinely include CA 15-3 determination before treatment of patients with invasive breast cancer.

As a nonconsensual approach required further in-depth evaluation, we were prompted to confirm the prognostic value of initial CA 15-3 concentration and to evaluate the impact of its determination on the therapeutic management of patients.

During a 5-year period, all consecutive women referred to HBC for the initial management of invasive breast cancer had a CA 15-3 assay before treatment. The patients with previous history of another type of cancer were excluded. Patients studied were followed up according to the standard procedures of HBC, for at least 54 months. Two thousand and thirty-six patients were included, with 200 test results >30 kU/l.

For each patient, criteria investigated were age, hormonal status, the breast (left or right) affected, histological classification and grade, tumour size (T), clinical lymph node invasion (N), presence or absence of hormone receptors and CA 15-3 concentration. Disease treatment and patient evolution data were also collected.

All CA 15-3 determinations were carried out at HBC, using a primary tube of blood collected on heparin, with a Kryptor® analyser (BRAHMS Hennigsdorf, Germany). The reproducibility ($n = 350$) was better than 6% for a concentration of 30 kU/l and 83 kU/l. The upper limit of the normal range is 30 kU/l.

Statistical tests were carried out with SEM software (Fabrice Kwiatkowski, Centre Jean-Perrin, Clermont-Ferrand, France). Differences between groups were evaluated using least-squares difference tests for quantitative characters and chi-square tests for qualitative characters. Survival curves were calculated by the nonparametric Kaplan–Meier method. Univariate analysis was carried out with Mantel–Haentzel tests (two curves) or log-rank tests (more than two curves). Cox models were used for multivariate analysis. A 5% threshold was considered significant.

During a 5-year period, 2036 patients attending the HBC for the initial management of invasive breast cancer underwent pretreatment CA 15-3 determination. Initial CA 15-3 concentration was >30 kU/l in 200 patients (9.8%), with 75 who had metastases at diagnosis (M+). Significant differences between the M+ and M− populations only concerned tumour size, clinical lymph node invasion and CA 15-3. Types of management and survival curves of patients with and without metastases were very different, therefore the M+ and M− groups were assessed separately.

An initial CA 15-3 concentration of >30 kU/l was associated with a poor prognosis: 75 of these patients (37.5%) had
metastases at diagnosis versus 46 of the 1836 patients (2.5%) with initial CA 15-3 concentrations <30 kU/L. Furthermore, in 19 of these 75 patients, metastasis diagnosis was based on complementary examinations not prescribed in the absence of determination of this marker.

In this population [overall survival (OS) 27.8 months], the only prognostic factors were age at diagnosis ($P < 0.02$), tumour size ($T1–T2/T3–T4$, $P < 0.03$) and, above all, the presence of hormone receptors ($P < 10^{-6}$).

Tumour size ($T1–T2/T3–T4$, $P < 0.04$), grade according to Scarff, Bloom and Richardson ($P < 0.04$), age at diagnosis ($P < 0.02$) and lymph node invasion ($P < 0.02$) were considered poor prognostic factors for OS. OS (54.5 months) was shorter for patients presenting several factors associated with a poor prognosis. Lymph node invasion ($P < 0.03$) was the only prognostic factor for disease-free survival (DFS). The presence or absence of hormone receptors did not have any prognostic value for this group.

In these patients, CA 15-3 concentration was a prognostic factor, with a threshold value of 40 kU/L (median of observed concentrations), both for DFS and OS (Figure 1A and B). CA 15-3 retained its prognostic value in all subpopulations defined in terms of classic prognostic factors, except those where a major factor indicative of a poor prognosis was present (T3/T4 and grade 3).

In multivariate analysis using Cox model, two factors were identified as independent prognostic factors in this population: pathological lymph node invasion (pN, $P < 0.009$) and pretreatment CA 15-3 concentration ($P < 0.04$). We were able to define three groups with distinct prognoses (CA 15-3 $> 40$ and pN+, CA 15-3 $> 40$ or pN+ and CA 15-3 $> 40$ and pN+). The ‘pN+ and low CA 15-3’ group had the best prognosis and the ‘pN+ and high CA 15-3’ group had the worst prognosis. The third group (pN−/high CA 15-3 or pN+/low CA 15-3) had an intermediate prognosis. These results included DFS (Figure 2) and OS.

Twenty-four of the 125 M− patients (19%) presented no factor associated with a poor prognosis (median CA 15-3 concentration 35.5 kU/L, range 31–53 kU/L). This isolated high level of CA 15-3 resulted in modification of standard treatment of 14 patients. The limited number of patients and events renders it impossible to draw conclusions as regards the efficacy of this management.

The poor prognostic value of high initial concentration of CA 15-3 in invasive breast cancer is well demonstrated. In this study, CA 15-3 concentrations <30 kU/L had strong negative predictive value for metastases at diagnosis (97.5%). Conversely, 37.5% of patients with initial CA 15-3 concentrations $> 30$ kU/L had metastases. Thus, a high initial CA 15-3 concentration led us to assess the possible spread metastases that would otherwise remain undetected and had contributed to the high percentage of patients with metastases on inclusion. Metastases were initially present in 121 patients, 46 of whom had normal CA 15-3 levels (42%). In 19 cases (16%), diagnosis of initial metastases would not be done without CA 15-3 determination. Therefore, this result has a direct impact on management of these patients, avoiding unnecessary invasive surgery. According to the American

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**Figure 1.** Survival curves for patients with CA 15-3 >30 kU/L and no metastasis at diagnosis (M−) as a function of initial CA 15-3 concentration, below (1, $n = 62$) or above (2, $n = 63$) the median value of 40 kU/L, used as the cut-off point. (A) Disease-free survival: mean disease-free survival 47.5 months (2) versus 61 months (1) ($P < 0.03$); (B) Global survival: mean overall survival 54.3 months (2) versus 37 months (1) ($P < 0.003$).

**Figure 2.** Disease-free survival curves for patients with no metastasis at diagnosis (M−), as a function of pathological lymph node invasion (pN) and CA 15-3 concentration ($P < 0.0005$). (1) pN0 and 30 < CA 15-3 ≤ 40 kU/L, $n = 22$, $m = 56.6$ months; (2) pN0 and CA 15-3 > 40 kU/L, $n = 19$, $m = 43.7$ months; (3) pN+ and 30 < CA 15-3 ≤ 40 kU/L, $n = 40$, $m = 53.6$ months and (4) pN+ and CA 15-3 > 40 kU/L, $n = 40$, $m = 33.5$ months.
Society of Clinical Oncology expert panel [1], a value 5–10 times higher than the upper limit of normal values is an indicator of probable metastases. In our experience, a value above the 30-kU/l threshold should prompt an active search for metastases.

In patients without metastases, we observed a high incidence of early recurrence when initial CA 15-3 concentrations were high: 58 cases among the 125 patients (46%), with a mean time to recurrence of 29.8 months, versus 419 of 1836 patients (23%, mean time of 30.9 months) in patients with a normal initial CA 15-3 concentration. These results confirm those of Park et al. [7].

For M− patients, an initial CA 15-3 level above the median for our population (40 kU/l) was associated with the poorest prognosis. Our results therefore confirm previously reported results [7–16] concerning the prognostic value of initial CA 15-3 concentration in patients without metastases at diagnosis. Cox model identified initial CA 15-3 concentration as an independent prognostic factor, the most important after lymph node invasion. These results also confirm those of several other clinical series [7, 14–17]. It should be stressed that these results were obtained in a population of patients with an initial CA 15-3 concentration >30 kU/l and cannot necessarily be transposed to an unselected patients population. This may explain why some studies have not recognised the independent nature of this factor [11, 13, 15, 18]. However, the prognostic value of CA 15-3 was probably masked in some studies by one of the other markers: carcinoembryonic antigen [13, 15] and ornithine decarboxylase [11]. O’Hanlon et al. [18] did not identify CA 15-3 concentration as an independent prognostic factor, but did attribute a positive predictive value: a 40-kU/l threshold produced 83% probability of advanced disease.

This study confirms the practical impact of the routine use of CA 15-3 determination at the time of initial breast cancer diagnosis. A CA 15-3 concentration >30 kU/l is associated with a poor prognosis and led us to an analysis of cancer spread and the search for metastases: 16% of initial metastases were diagnosed on the basis of isolated high CA 15-3 level. These metastases would otherwise go undetected and unnecessary invasive surgery could be carried out. In the nonmetastatic patients, an initial CA 15-3 concentration >40 kU/l was found to be an independent factor associated with poor prognosis, even in the subpopulations studied, except those with a very poor prognosis (T3/T4 or grade 3).

The prognostic value of initially high CA 15-3 level in patients with invasive breast cancer has been widely demonstrated. Our results strongly indicate that its determination could be considered a useful tool, which must be integrated in the initial routine staging investigations, as recommended by O’Hanlon et al. [18] who wrote in 1995: ‘We recommend the routine use of this marker in the preoperative assessment of primary breast cancer’.

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