

**A COST-UTILITY ANALYSIS OF FIRST-LINE CHEMOTHERAPY
REGIMENS IN THE TREATMENT OF METASTATIC
BREAST CANCER AFTER ANTHRACYCLINE FAILURE**

K. Le Lay ⁽¹⁾, S. Payet ⁽¹⁾, L.Riou-França ⁽¹⁾, N. Chemali ⁽³⁾, R. Launois ⁽¹⁻²⁾.

(1) REES France, 28 rue d'Assas, 75006 PARIS, France, tel /fax : 33 (0)1.44.39.16.90 / 92,
reesfrance@wanadoo.fr, <http://www.rees-france.com> ; (2) Université de Paris XIII, France; (3) Lilly France.

ABSTRACT

OBJECTIVES : Four chemotherapy regimens: gemcitabine-paclitaxel (Gem/Pac), paclitaxel in monotherapy (Pac), docetaxel in monotherapy (Doc) and docetaxel-capecitabine in association (Doc/Cap), are commonly used in the first-line treatment of metastatic breast cancer after anthracyclines failure. The purpose of the study is to rank these strategies for the French health system according to their incremental cost-utility ratios. **METHODS:** A Markov model was developed based on the results of efficacy and tolerance of three recently published phase III studies. Ravdin and al (2003) showed superiority for docetaxel (Doc) compared to paclitaxel (Pac) in monotherapy. O'Shaughnessy and al (2002) for the Doc/Cap regimen and the phase III registration study for the Gem/Pac (2003) showed superiority for Doc/Cap and Gem/Pac compared to monotherapies, Doc and Pac respectively. Probability transitions were obtained from the median survival, time to progression and median response duration published. The costs were calculated by adding DRG costs, onerous drug costs reimbursed over DRGs and transportation expenses. Costs of febrile neutropenia, blood transfusions, nausea and vomiting, diagnosis and palliative care, were taken into account. **RESULTS:** The Gem/Pac strategy appears to be the most effective compared to Doc, Pac and Doc/Cap. In terms of survival, Gem/Pac has an additional efficacy of 16.9 weeks and an incremental cost of 5,586 € compared to Doc/Cap, with a incremental cost-effectiveness ratio (ICER) of 17,160 € per year of life gained. In terms of survival adjusted to quality of life, the efficacy gain is 12.8 weeks and the ICER is 21,200 € per year of life gained. When the D8 gemcitabine is administered in a home hospitalisation setting, the Gem/Pac ICER is 14,590 € year of life gained. **CONCLUSION:** The incremental cost-effectiveness ratios of Gem/Pac regimen are between 10,000 and 22,000 € per year of life gained, still below the limits recognized as reasonable at the international level. Another advantage of the Gem/Pac combination therapy is to allow home care on day 8 of the cycle.

1. INTRODUCTION

Every year 42,000 new cases of breast cancer are diagnosed in France. 20% of cancers are attributed to breast cancer. In 1999, tumor mortality represented approximately one-quarter of the deaths in women, all ages combined¹; thus we deduce that breast cancer is responsible for one out of every 20 deaths in the French female population. This figure justifies using every possible measure for prevention, for managing patients in an increasingly appropriate manner, and for developing effective and well-tolerated innovative treatments. The five-year survival rate, all stages combined, is currently 73%, and the percentage of patients surviving at 10 years is nearly 60%². The treatments depend on the stage of the disease at the time of diagnosis and include hormone therapy, surgery, radiation therapy, and chemotherapy. Most often, these therapies are combined to fit the patient profile, based on her treatment response. Thus, new drugs have been developed in recent years to provide an answer for patients in treatment failure with anthracyclines. These include vinorelbine and taxanes, sometimes in combination with capecitabine or gemcitabine. The latter has proven effectiveness in combatting many solid tumors and its action is accompanied by low toxicity³. The use of gemcitabine as a first-line treatment for metastatic breast cancer has been described in numerous phase I and II trials in populations of 20 to 50 patients. In those studies, gemcitabine was administered alone⁴⁻⁶ or in combination with doxorubicin,⁷ cisplatin,⁸⁻⁹ vinorelbine¹⁰, epirubicin¹¹, paclitaxel¹², or docetaxel¹³. Larger phase III trials have begun more recently and there are few publications. The cost of managing a breast cancer patient from diagnosis through terminal care is high. However, they are difficult to evaluate, as evidenced by the medical economic studies on the subject¹⁴. The objective of this study is to evaluate the efficacy and cost of treatment with gemcitabine in combination with paclitaxel, as first-line treatment for metastatic breast cancer, after failure of chemotherapy with anthracyclines. The results of an important study¹⁵, completed in 2004, involving gemcitabine in combination with paclitaxel, should prove useful. The comparator in that study was paclitaxel alone. The method chosen to achieve our objective is to construct a model to compare these two strategies from the standpoint of efficacy and expenses incurred. Two therapeutic options commonly used in the indication have been added : docetaxel alone compared to paclitaxel alone in a recent study conducted by Ravdin¹⁶, and the association of docetaxel and capecitabine, which is the natural comparator for the gemcitabine-paclitaxel combination, documented in a phase III trial published in 2002 by O'Shaughnessy¹⁷.

2. METHODS

2.1 Treatments and administration regimens

A Markov model has been constructed based on the results of efficacy and tolerance of the three recent studies on metastatic breast cancer. In Ravdin's trial ¹⁶, the two treatment arms were docetaxel alone on D1 at a dose of 100 mg/m² and paclitaxel alone on D1 at a dose of 175 mg/m². The superiority of docetaxel over paclitaxel was significant in terms of overall survival and median time to progression. The results of the JHQG study¹⁵ made it possible to document the efficacy and tolerance of gemcitabine 1250 mg/m² on D1 and D8 in combination with paclitaxel 175 mg/m² on D1, versus paclitaxel 175 mg/m² alone on D1. The reference arm in the O'Shaughnessy study¹⁷ was docetaxel 100 mg/m² on D1, to which the capecitabine-docetaxel combination, i.e. 1,250 mg/m² x 2 from D1 to D14, and 75 mg/m² on D1, was compared. In both cases, the combination of two agents significantly improved survival and response compared to the taxanes alone, whence the interest of comparing these combinations in a simulation. Each of the chemotherapy protocols was conducted in 3-week cycles.

2.2 Type of economic study used

In the three reference studies, significantly different efficacies were found among the therapeutic regimens, whether it be among the objective response rates (RR), the median survival duration (MSD), the median time to progression (TTP) or the median response duration (MRD). These statistically significant comparisons involve capecitabine-docetaxel vs docetaxel alone, docetaxel vs paclitaxel, gemcitabine-paclitaxel vs paclitaxel in monotherapy. Since the costs of acquiring these chemotherapies are also different, a cost-effectiveness analysis will make it possible to classify the four treatment arms in comparison to each other based on an efficiency criterion ^{14,20,21}.

2.3 Structure of the model

Each of the treatments was analysed using Markov's cyclic tree diagram process where a group of patients moves in a repetitive way into a specific number of mutually exclusive states of health^{14,22}. This is designed with the simulation lasting 5 years on the basis of weekly cycles. This pace of simulation is more suited to modeling the skipped doses that occur due to acute toxicity at the start of treatment. Nine states were singled out: induction of treatment

(Induction), Skipped Dose (SD) and Reduction dose of 25 or 50% (RD75, RD50) after severe toxicities, after the Tumor Extension Assessment, the remission (REM) and the remission in presence of neurotoxicities (REM-NT), avoidance of treatment (PD), drop-out from the study (DO) and death (D). For each one-week cycle, the model provides for actualizing the costs and efficacy and utility criteria, of discount annual rates of 3.5% and 1.5% respectively, based on the recommendations of the National Institute for Clinical Excellence (NICE)²⁶. At the end of simulation, the annual follow-up costs per patient for the French health system of these four therapeutic options can be compared whilst the total time of survival and remission may be used to evaluate the therapeutic benefit of these strategies, according to two possible criteria : overall survival, progression-free survival measured as weeks spent in the model. These two points of view have been supplemented by a third alternative : Reasoning in terms of QALYs makes it possible to assign an entire range of efficacy values to the different states of health in the model.

2.4 Clinical parameters

- Efficacy data

Our model uses median survival duration (MSD), median time to progression (TTP), and median response duration (MRD) with their limits and significance, since they are particularly well documented. The chemotherapy with gemcitabine provides the best results in terms of overall survival, with an MSD of 74 weeks, versus approximately 60 weeks for the other combination and for the single-drug therapies (46 and 50.8 weeks for docetaxel and paclitaxel, respectively, table 1) according to the most pessimistic results. The TTP in the capecitabine-docetaxel arm was the longest, with 24.4 weeks separating the start of treatment and relapse in 50% of the patients. The gemcitabine-cisplatin combination was in the same order of magnitude with a TTP of 21.6 weeks, i.e., fewer than 3 weeks' difference. This is a clear advantage over paclitaxel, whose TTP is about 14 weeks. Thus, the combination of gemcitabine with that agent decisively contributes to the efficacy of the therapy. Finally, it is difficult to situate the docetaxel arm, whose TTP is estimated at 16.8 and 22.8 weeks, according to our two sources. The median response time was also longer in the arms combining two agents. Remission lasted more than 35 weeks in half of the patients, versus 28.8 weeks in the paclitaxel alone arm, i.e., a benefit of one and an half months for the patients treated with gemcitabine. The response rate in patients who received the combination was significantly higher than in the control group. These results unambiguously classify the gemcitabine-paclitaxel strategy at the top with respect to efficacy. A secondary criterion, such

as 1-year survival, provides another illustration of this. Nearly three-quarters are survivors 1 year after the start of the study, versus 61% of patients treated with paclitaxel alone. Finally, the drop out (DO) rate is 12.9% of patients randomized to docetaxel in the Ravdin study (6% in the O'Shaughnessy study), and 6.3% of patients receiving paclitaxel. The paclitaxel arm in the JHQG study shows 5.1% drop outs. This rate was 5.6% in the gemcitabine-paclitaxel.

- Tolerance data

For each of the four therapeutic approaches, we took the parameters needed to model side effects from published data : incidence, nature and severity of side effects, classified according to the WHO toxicity scales. The side effects recorded in all cases were nausea and vomiting, haematological toxicity, and in particular the incidence of febrile neutropenia requiring admission to hospital. Certain frequent types of toxicity do not involve any particular costs (drugs, hospitalization, etc.); therefore, we decided not to include the toxicity if it consisted of alopecia or asthenia, in order not to penalize any strategy.

The most commonly encountered grade 3 or 4 toxicities, regardless of the treatment are, were hematologic toxicities and neutropenia in particular. Nearly all (93%) of the patients treated with docetaxel alone in the 2003 Ravdin study presented neutropenia at a frequency much higher than in the O'Shaughnessy trial (15%). 48.6% of patients receiving gemcitabine-paclitaxel developed such toxicity. With paclitaxel alone, we found a neutropenia rate of 11% in the 2003 Ravdin study and 55% in the JHQG trial. Few cases of febrile neutropenia or infections were reported with treatments comprising paclitaxel. There were between 15 and 21% in the docetaxel alone arm and 16% in the capecitabine-docetaxel arm. 3.4% and 8.2% of patients treated by paclitaxel and gemcitabine-paclitaxel, were transfused. The percentage seems to be on the same order of magnitude in docetaxel arm, since 10% of the patients had severe anemia, a complication that often requires transfusion. However, no anemia was reported in the O'Shaughnessy study. Grade 3 or 4 nausea and vomiting affected 8% of patients receiving docetaxel and nearly 3% in the other arms. Finally, severe neurotoxicity affected between 4.3 and 8% of patients receiving paclitaxel, 8.4% of patients treated with the gemcitabine-paclitaxel combination, and 12% in the docetaxel alone arm (motor and sensory neuropathies combined). Furthermore, toxicity results in drop outs from the trial and dosage adjustments. Dosage adjustments affect 25% of cycles and approximately 13% for the docetaxel alone and gemcitabine-paclitaxel arms, respectively. Again, according to this study, there were 2 to 6% of cycles with dosage reductions in the paclitaxel arm. We likened the cycle percentages to patient percentages, which is correct, since we are reasoning in means.

Based on the results of the references study, the three most common types of acute severe toxicity were used in each arm : for the gemcitabine-paclitaxel arm, neutropenia, leukopenia, and blood transfusion ; for the docetaxel alone strategy, neutropenia, gastrointestinal disorders (including nausea, vomiting, diarrhea, and stomatitis), and febrile neutropenia ; for paclitaxel alone, neutropenia was the most common toxicity, followed by anemia, which was grouped with transfusions to facilitate interpretation of the 2 studies and, finally, gastrointestinal disorders. The frequencies of the cumulative toxicities used in the model for each of the arms are given as percentages of motor and sensory neuropathies combined.

- **QALYs**

The weight factors were derived from a 1997 cost-utility study on metastatic breast cancer¹⁴, using Standard Gamble technics, where the impact of treatment response on quality of life and the interaction of response and toxicity phenomena in evaluating patient quality of life were accurately factored in. We assigned efficacy values based on the results of that study. During the first course, efficacy equals 1. It decreases to just 0.6 for withdrawals from treatment within the first 2 weeks, 0.63 when there are acute grade 3 or 4 toxicities, and 0.52 when the patient progresses and terminal care progressively replaces chemotherapy. Furthermore, when the patient is in remission, it has been shown that his quality of life is greatly altered by neuropathy-type cumulative neurologic toxicities. Thus, we weighted the efficacy associated with the "Remission with Neurotoxicity" state by a factor of 0.66. A bonus of 5% has been applied to patients undergoing chemotherapy at home, based on patient comfort, since it avoids a round-trip to the hospital, the stress induced by a change of environment, and also a degree of disincentive caused by contact with patients in more advanced stages of disease.

2.5 Economic parameters

The cost of administering chemotherapies and of treating any complications were estimated from the French health insurance perspective in 2005^{27,28}. The resources used in hospital for each course were calculated from a PMSI approach by summing the DRG tariff "chemotherapy for less than 48 hours" and the price of high cost compounds paid additionally in the context of the T2A (tariff-based activities)^{28,29}. Costs of chemotherapy in a home hospitalisation were estimated using the HH tariff model³⁰. A research for the most appropriate DRG was used to calculate the costs of managing the 3 groups of severe toxicities studied and integrating the cost of diagnosis and palliative care in cases of progressive

disease³⁴. The return transport costs from hospital to home were included³¹. Direct non medical and indirect costs were excluded from the scope of the analysis

☞ **Cost of acquiring chemotherapy**

The cost of the expensive chemotherapies being studied results from the list of high-cost pharmaceuticals products published per conditioning unit (UCD) in the Official Journal on December 31, 2004³²⁻³⁴. These tariff costs are the sales prices stated by companies or based on the fixed calculation by the French Comité Economique des Produits de Santé (CEPS, Health Care Products Economic Committee), raised by VAT at 2.1%. Capecitabine is not on the list of high-cost drugs, the price of one 150 mg tablet is 1 €, and the price of one 500 mg tablet is 3.33 € (GERS). The price per milligram is particularly high for the taxanes, more than 8.8 € HT for 1mg of docetaxel and 4.26 for the paclitaxel, and of 0.20 € HT for gemcitabine. In the setting of centralized preparations in pharmacies²⁷, the units of conditioning are fractionned in milligram. The quantities of each cytotoxic agent were thus calculated starting from an index of body surface average of 1,7 m² and doses recommended according to whether the dosage is managed entirely or to 75 or 50% of the initial dosage after which has occurred of toxicities. Certain drugs as gemcitabine can be delivered by a pharmacy duly authorized³³ of a public hospital for an administration at home in the setting of a private home-hospitalization (HH) structure (57.2% of the structures of HH), a 15% on costs margin is then deducted per prescription line³⁴.

☞ **Administration costs of chemotherapies in hospital**

To the cost of treatment (table 2), we add the DRG “8300” for a chemotherapy session in a day hospital (424.17 € in 2005²⁹). Each course of chemotherapy involves the patient traveling to the hospital and then returning home. Assuming a mean distance of 30 km [18 miles] from home to hospital, in view of the costs of the method of transportation used³¹ (LRV, ambulance, taxi, or private car) weighted by the frequency of use of such vehicles and incorporating the regional fees applicable to medical transportation and mileage compensation paid for use of a private care, the mean cost of a transportation from home to hospital was estimated at 82.97 €.

☞ **D8 Home Care for gemcitabine alone**

The second administration of gemcitabine in D8 can be carried out in a home-hospitalization setting, contrary to the taxanes which require a particular monitoring. The tariff and the

regulation context of the structures and establishments practising the home medical care has defined recently in the activity tariffs legislative and regulatory framework (T2A)³⁰. The 31 daily fixed prices of stay and care, called Groupes Homogènes de Tarifs (GHT, Tariff Reference Groups) results from weightings associated with the combinations authorized with five variables : the primary diagnosis, the associated diagnosis, the level of dependence measured by the index of Karnofsky, duration of the hospitalization, the statute of the establishment. The daily tariff of a home medical care, with chemotherapy and treatment of the pain, for a patient-type presenting a mild dependence (Karnofsky 70-80%), taken charges some during less than 5 days, rises in a public/PSPH establishment and a private establishment, with 198.1 € and 197.83 € respectively. By using the proportion of the private and publics/PSPH home medical care having taken part in IRDES study, of 42.8% and 57.2% respectively, this daily tariff rises for all establishment combined with 197.94 €. This one replaces the cost of a administration of chemotherapy during a day hospitalization and of the transport residence-hospital. The cost of chemotherapy acquisition remains in charge of the health insurance. For a cycle of the arm gemcitabine-paclitaxel, taking into account all the cost factors calculated until now, we obtain a total cost of 2,925 € instead of 3,178 € with a traditional day hospitalization. The saving made rises with more than 1,512 € per patient receiving 6 cycles of chemotherapy.

☞ **Costs of treating toxicities and cost of terminal care**

The DRGs used for acute hematologic toxicity, acute gastroenterologic toxicity, and cumulative toxicity are shown in table 4. We hypothesize that 10% of patients who develop grade 3 or 4 toxicity are hospitalized. These are the most severe cases. Therefore, certain DRGs with Complications and Co-Morbidities (CCM) were selected²⁹. A cost of transportation between home and hospital was deducted at each time³¹. The cost of providing terminal care to patients was taken from DRG 7965 "Palliative care, with or without procedure," with a fare of 6,664 €²⁹.

2.6 Probabilistic sensitivity analysis

Twelve variables of the model have a value which can be subjected to uncertainty³⁶⁻³⁷. Within the framework of a montecarlo of second order, each one of these variables was characterized by a distribution. The index of Body Surface was represented as normally distributed variable with an average of 1.7 m² and 99 % of the values are at ± 20 % of this average. The cost of transport is related to two parameters: the number of kilometers and the type of transport

used. The IRDES report in 1997 gave us the average distances between 15 and 45 kilometers. A first normal distribution around a central value of 30 km, and a distribution of Dirichlet which makes it possible to ensure that the sum of the rates of types of transports used is always equal to 1, give at the end of a parametric bootstrap, a normal distribution of average 82.97 € and standard deviation 12.53 €. In the IRDES database, there were 3,228 structures of home-hospitalizations (HH), where the private establishments accounted for 1,847 HH and the publics/private non for profit establishments for 1,381. The proportion of public HH structures was thus characterized by a beta distribution (3,228;1.47). Beta distributions, defined by two parameters: r the number of events, and n the total number, and bound between 0 and 1, are well adapted to characterize proportions. Median durations are generally characterized by skewed distributions extended towards the right. The Lognormal distributions making it possible to simply express the quantiles according to its parameters, it was retained to characterize the three median times published (table 5). The probabilities of early stops of treatment (DO), of reductions of doses (RD), of apparition of severe toxicities, will be described starting from the rates observed by Beta distributions. Concerning monotherapies for which each clinical parameter is available in two clinical trials, a mix of distributions was performed, taking into account the number of patients observed in the two studies for the same arm. A 5000 point simulation allowed us to determine the confidence limit of the resulting costs and outcomes for each strategy. The corresponding cost-effectiveness acceptability curves were presented ³⁶⁻³⁸.

3. RESULTS

3.1 In terms of survival

At the end of simulation in terms of survival, paclitaxel and docetaxel appear with a lower efficacy than that of the two associations and are more expensive than the capecitabine-docetaxel. The two associations remain in list, with an additional efficacy of gemcitabine-paclitaxel of 16.9 weeks of life gained and an overcost of 16,976 € per year of life compared to the capecitabine-docetaxel. The cost-effectiveness ratio of the gemcitabine-paclitaxel is the largely lower than the internationally recognized threshold of 50,000 € per year of gained life, that is to say 959 € per week of life (table 6).

The representation of 5,000 points ($\Delta C, \Delta E$) on the cost-effectiveness plane makes it possible to better take into account of the outliers (figure 1). If one observes the 5,000 values of the paclitaxel compared to the capecitabine-docetaxel (figure 2), 50.4% of values show a

superiority of efficacy of paclitaxel (points to the right of the light dotted line) and 49.6% of them show with a $\Delta E < 0$, what illustrates well the confidence interval extended towards the two directions (table 5). The paclitaxel is equivalent in term of efficacy with half of the points on each side of the threshold ΔE and in each 5,000 cases, more costly than the association of capecitabine and docetaxel. If one observes the values of gemcitabine-paclitaxel compared to capecitabine-docetaxel (figure 3), there is a small proportion of cases where $\Delta E < 0$ (61/5,000, i.e 1.2 %, points to the left of the light dotted line), 297 points (5,9%) correspond to $\Delta E > 0$ and $\Delta C/\Delta E > 959 \text{ €/week}$ (points between the light and the dark dotted lines) and 4642 points (92,8%) are below the threshold of 50,000 €/ year α 959 €/week (points to the right of the dark dotted line). The probability that the gemcitabine-paclitaxel association is acceptable compared to the other association with the 959 €/week threshold of life gained is then 93 %.

The corresponding acceptability curves are presented in figure 4. Until the willingness to pay of 246 € per week of life gained, the capecitabine-docetaxel arm is the strategy which has the highest probability of being cost-effective. Between 246 € and 357 €, the paclitaxel arm is the most acceptable strategy with a probability of being cost-effective inferior to 0,4. If the willingness to pay is higher than 357 € / week (20349 € per year of life gained) the gemcitabine-paclitaxel strategy stays the most cost-effective one.

3.2 In terms of quality of life-adjusted survival

In terms of quality of life-adjusted survival, the paclitaxel allows a small gain of efficacy of 0,9 weeks in comparison to the association capecitabine-docetaxel with an additional cost of 550 €, what results in a cost-effectiveness ratio of 31,777 €. The gemcitabine-paclitaxel appears compared to paclitaxel, with a gain of 12.8 weeks and an overcost of 5,036 €, i.e. a ratio of 20,458 € per quality-of-life adjusted survival. Compared to capecitabine-docetaxel, this gain of efficacy is of 13.7 weeks, i.e. an ICER of 21,202 € per quality-of-life adjusted survival. The cost of a year of life gained when passing from the paclitaxel alone arm to the gemcitabine-paclitaxel arm is higher than in the overall survival analysis, as is the case with any quality of life-adjusted analysis. In fact, we give less value to weeks spent in "deteriorated" states of health. Therefore, at an equal cost, it becomes difficult to achieve the same efficacy result. However, with a higher degree of strictness, the ICER ratio of 21,202 € per year of life remains two times below the 50,000 € limit declared acceptable in the preceding section (table 6).

If one observes the representation (ΔC ; ΔE) points, the paclitaxel appear quasi-equivalent in term of quality of life-adjusted survival compared to the capecitabine-docetaxel with a half of the points on each side of the threshold ΔE equal to 0 and, in each 5,000 cases, more costly than the association. The paclitaxel strategy may be advantageously replaced by a combination of the capecitabine-docetaxel and gemcitabine-paclitaxel strategies, what is called a weak dominance phenomenon. The 5000 points obtained by the comparison of the gemcitabine-paclitaxel with the capecitabine-docetaxel are mainly (95.3%) located in the cost-effectiveness quadrant where $\Delta E > 0$ and $\Delta C/\Delta E < 959 \text{ €/week}$ (to the right of the dark dotted line, figure 5). There is a small proportion of cases (0.26 %) where $\Delta E < 0$, and 4.4% points where $\Delta C/\Delta E > 959 \text{ €/week}$. The probability that the gemcitabine-paclitaxel is acceptable compared to the capecitabine-docetaxel with the 959 €/week threshold is then 95 %. As shown in corresponding acceptability curves (figure 6), until a willingness to pay of 216 €/week, the capecitabine-docetaxel strategy is the one which has the highest probability of being cost-effective. Between 216 € and 492 €, the paclitaxel arm appears as the best choice. If the willingness to pay is higher than 492 €/week (25,584 € / year of life gained), then the association of gemcitabine and paclitaxel become the most cost-effective strategy.

3.3 Advantage of home care for D8 of Gemzar®

We replaced the chemotherapy session for administration of gemcitabine on D8 in a day hospital with home care. In terms of overall survival, the ICER ratio passes from 17,160 € to 14,585 € per year of life gained by choosing to administer gemcitabine on day 8 of the cycle at the patient's home, rather than at the hospital (table 7). The gain is thus 16% compared to the "D1 and D8 day hospital" option. This is explained by the elimination of the round trip between home and hospital, replacing it with a more Home-Hospitalization day price that is more advantageous than billing for a "chemotherapy session" DRG, and by the increased efficacy, which we assume to be 5%. For the common ceiling ratio of 50,000 € per life year gained (959 € per life week gained), the probability that gemcitabine-paclitaxel is cost-effective is 83.3%. Until a willingness to pay of 237 €, the capecitabine-docetaxel strategy is the one which has the highest probability of being cost-effective. Between 237 € and 294 €, the paclitaxel arm is the best choice. If the willingness to pay is superior to 294 €, then the gemcitabine-paclitaxel strategy is the most cost-effective one.

4. DISCUSSION

Whereas the natural comparator of the gemcitabine-paclitaxel association is the capecitabine-docetaxel association, we have not found any trial comparing them head to head. Instead, we disposed of two trials comparing these association therapies to either paclitaxel or docetaxel and one other trial comparing these two single-agent therapies. In absence of a clinical trial making direct comparisons between the four therapeutic options, an analysis of the therapeutic benefit and costs of these four treatments was carried out indirectly by developing a Markov model which was as simple as possible. This model has been constructed based on the results of efficacy and tolerance of the three most recent studies in the treatment of metastatic breast cancer¹⁶⁻¹⁸: JHQG 2003, Ravdin 2003, and O'Shaughnessy 2002. The three clinical trials have common inclusion criteria. The patients enrolled were all adults with inoperable breast cancer with a local or metastatic relapse. They received adjuvant / neoadjuvant chemotherapy containing anthracyclines, but no prior chemotherapy in the metastatic phase. Their laboratory values were normal and their medullary reserves sufficient. The median age of the patients in the three studies combined, calculated by weighting the populations, was 53 years.

Five types of clinical data have been introduced into this model: median survival, time to progression, median response duration, drop-outs, reduction doses to characterise the clinical change in assessable patients. As knowledge currently stands, the relation between response rate and survival has not been demonstrated. This traditional parameter was not used. After 5 years of simulation, the percentages of deceased patients are 96.3%, 97.2%, 96.5%, and 92.5% in the capecitabine-docetaxel (1), docetaxel alone (2), paclitaxel alone (3), and gemcitabine-paclitaxel (4) arms, respectively. Thus, the 5-year survival rates were considerably lower than those generally found with this disease, as we stated in the introduction. The patients enrolled in the study were in the metastatic phase and, thus, already at an advanced stage of the disease. The median time since the diagnosis of breast cancer was 29 months, i.e., approximately 2 and a half years, in the O'Shaughnessy study¹⁷. This same median time was 34.3 months in the gemcitabine-paclitaxel arm of the JHQG study¹⁵, and 29 months in the paclitaxel alone arm. Thus, the high mortality after 5 years of follow-up is not surprising. A Markov analysis of arms 1 and 4, corresponding to the 2 combination therapies, makes it possible to verify that the percentage of deceased patients was 50% after 58 weeks in the capecitabine-docetaxel arm and after 74 weeks in the gemcitabine-paclitaxel arm. Furthermore, by looking at the contributions of the different state of health to the total

efficacy of each strategy, we can better appreciate the advantage of the latter chemotherapy. Nearly 50% of the time spent in the model, excluding withdrawals from treatment, was spent in the "remission" state in arm 4. Patients in remission continued to undergo the treatment (up to a limit of 15 weeks), which partially explains the high cost of the strategy. In comparison, the percentage of weeks spent in the "remission" state was 33.6% for patients in the capecitabine-docetaxel arm.

To deal with the fact that two trials were available for both monotherapies paclitaxel and docetaxel, we adapted our probabilistic sensitivity analysis. Instead of choosing by chance one of the two trials for each monotherapy, with the corresponding outcomes' densities of probability, we combined the two densities for each outcome and each monotherapy. The way the combination was done depended on the numbers in each treatment arm: the density of probability obtained from the most numerous trial was more frequently used to calculate the combined density of probability. This way all the information available for docetaxel and paclitaxel was taken into account and the weight of each trial in this information was proportional to its number of patients. Another method could have been considered. Indeed Mixed Treatment Comparisons models can greatly deal with indirect comparisons and are mainly used to combine information from several sources³⁹. In our case it would have been possible to simultaneously assess the effect of the four therapies compared on survival (or on any other outcome), even if all the pairwise comparisons are not available⁴⁰. The mechanism is the following : i) to assess the differential effect of gemcitabine-paclitaxel compared to paclitaxel alone in the first trial, ii) to assess the differential effect of paclitaxel compared to docetaxel in the second trial, iii) to assess the differential effect of docetaxel compared to capecitabine-docetaxel in the last trial, iv) and to combine the three differential effects (either sum or multiply them, depending on the type of effect measured). It is then possible to obtain the differential effect of gemcitabine-paclitaxel compared to capecitabine-docetaxel. A bayesian meta-analysis by Markov Chain Monte Carlo could do the deal. Nevertheless, this solution has not been chosen for the moment. We dispose of too few trials for each strategy to conduct a robust MTC: this kind of model is greatly dependent of the baseline assumptions of each study combined⁴¹. We are therefore looking for other studies comparing these strategies to conduct such an analysis.

The warnings about the reference studies were taken into account in the analysis. We conclude that single-drug therapies only are affected and likely to interfere with classification

of the different strategies. For example, the docetaxel alone strategy was strongly dominated in all cases in point, except when the Ravdin data is incorporated into the model. We could then consider doing a so-called "cost minimization" study between the two single-drug therapies, rather than a cost-effectiveness study, by postulating that the superiority of one over the other is not always evident, in terms of efficacy. Since the natural comparator of the 'gemcitabine-paclitaxel' combination is the other combination chemotherapy, capecitabine-docetaxel, the choice of the single-drug therapy parameters has no impact on our results and recommendations. In general, combinations are preferable to single agents and, of the combinations, the combination of gemcitabine with paclitaxel has greater efficacy at a low to moderate excess cost. Furthermore, in the O'Shaughnessy article, we note a large number of patients with dosage reductions and even withdrawals from one of the treatments in the capecitabine-docetaxel arm. When the withdrawal involved docetaxel, the patient remained in the study, but when capecitabine was discontinued, the patient dropped out of the trial. The manner in which the results were presented in the article does not inform us of the median survival times and median times to progression for these subgroups of patients. However, since the intermediate results of the JHQQ gemcitabine-paclitaxel study were very well documented, the parameters used to simulate the outcome in patients receiving gemcitabine-paclitaxel are more reliable. The gemcitabine-paclitaxel strategy appears in successive sensitivity analysis with ICER ratios situated in relatively limited ranges, between 10,000 € and 22,000 €. An advantage of this combination therapy is that it allows home care on day 8 of the cycle. We have seen that this option spares the patient travel and additional stress, while the costs incurred are lower. The benefit is thus twofold, and this type of chemotherapy should be encouraged. Based on the principle that the most effective treatment should be administered, it is very encouraging to note that the excess cost it incurs is limited compared to the strategies that are usually used. The higher cost essentially stems from the additional weeks spent in remission and, therefore, in treatment. It is a direct result of superior efficacy. This is a common problem with this type of analysis, where the least costly strategies are associated with high rates of mortality and withdrawal from treatment.

Tables and figures :

Table 1. Efficacy and tolerance data from the three reference studies

	Cap+Docetaxel	Docetaxel		Paclitaxel		Gem.+Paclitaxel
Study	O'Shaughnessy ¹⁷	O'Shaughnessy ¹⁷	Ravdin ¹⁶	Ravdin ¹⁶	JHQG ¹⁵	JHQG ¹⁵
Population	255	256	225	224	262	267
Efficacy						
MSD (weeks)	58* [49.2-65.2]	46 [39.2-50.8]	61.6*[53.2-74.4]	50.8 [42.4-59.2]	63.2 [57.6-69.6]	74* [66-84.8]
TTP(weeks)	24.4*.[21.6-26]	16.8 [13.6-18]	22.8* [18.4-27.6]	14.4 [12.4-16.8]	14 [11.6-16]	21.6* [18.4-24.4]
MRD (weeks)	29.2 [27.6-33.6]	28 [23.2-32]	-	-	28.8 [27.2-34.4]	35.2 [29.6-40.8]
RR (%)	42 [36-48]	30 [24-36]	37.4*	26.4	25,6[25-29]	39,3* [33.5-45.2]
DO (%)	10	6	12.9	6.3	5.1	5.6
Hematologic toxicities						
Neutropenia (%)	16	15	93	55	10.8	48.5
Febrile neutropenia (%)	16	21	15	2	1.2	5
Leukopenia (%)					1.5	10.6
Anemia (transfusion, %)			10	7	2.3 (3.4)	6.8 (8.2)
Non-hematologic toxicities						
Nausea (%)	6	2	5	3	1.5	1.1
Vomiting (%)			3	0	1.9	1.9
Diarrhea (%)	14.4	5.4	5	1	1.9	3.1
Motor neuropathy (%)			5	2	0.8	2.7
Sensory neuropathy (%)	24	1	7	4	3.5	5.7
RD (% of cycles)			25	6	2	G : 8.1 ; T : 5.2

* Significant difference at the 5% threshold :Cap-Doc vs. Doc; Gem-Pac vs. Pac; Doc vs. Pac

Table 2. Administration cost in hospital (€)

	Arm	Acquisition	Administration	Transportation	Cost/ cycle	Cost / week
1	Cap/Docetaxel	1,145	424.17	82.97	1,653	551
2	Docetaxel	1,527	424.17	82.97	2,035	678
3	Paclitaxel	1,295	424.17	82.97	1,803	601
4	Gem/Paclitaxel	2,163	848.34	165.94	3,175	1,059

Table 3. Toxicity DRGs used in the model

Adverse Event	DRG	Fare (€ ₂₀₀₅)
Febrile neutropenia	6759 Septicemia, age > 17 years with CCM	5,515.31
Neutropenia, leukopenia	6151 Reticulo-endothelial or immune system conditions without CCM	2,572.79
Anemia	6155 Erythrocyte line disorders, ages 18 to 69 without CCM	2,260.08
Transfusion	8306 Transfusions in sessions	682.6
Digestifs disorders	2104 Gastroenteritis and miscellaneous diseases of the digestive tract, ages 18-69 with CCM	3,040.64
Neurotoxicities	167 Other nervous system conditions, age < 70 years without CCM	2,265.09

Table 4. Distributions

Arm	Cap/Docetaxel	Docetaxel		Paclitaxel		Gem./Paclitaxel
Study	O'Shaughnessy	O'Shaughnessy	Ravdin	Ravdin	JHQG	JHQG
MSD	LogN(4,136;0,082)	LogN(3,905;0,080)	LogN(4,195;0,099)	LogN(4,003;0,090)	LogN(4,2242;0,049)	LogN(4,3809;0,0707)
TTP	LogN(3,272;0,061)	LogN(2,895;0,105)	LogN(3,200;0,106)	LogN(2,743;0,080)	LogN(2,7142;0,093)	LogN(3,1486;0,0801)
MDR	LogN(3,451;0,073)	LogN(3,407;0,094)	LogN(3,472;0,127)	LogN(2,981;0,141)	LogN(3,4354;0,092)	LogN(3,1486;0,0865)
DO	Beta (255,25)	Beta (256,15)	Beta (225,29)	Beta (224,14)	Beta (262,13)	Beta (267,15)
RD	Beta (255,166)	Beta (256,92)	Beta (225,56)	Beta (224,13)	Beta (262,5)	Beta (267,35)
Tox C	Beta (255,61)	Beta (256,3)	Beta (225,29)	Beta (224,11)	Beta (262,11)	Beta (267,22)
Tox 1	Beta (255,96)	Beta (256,38)	Beta (225,209)	Beta (224,123)	Beta (262,28)	Beta (267,129)
Tox 2	Beta (255,41)	Beta (256,32)	Beta (225,54)	Beta (224,16)	Beta (262,15)	Beta (267,28)
Tox 3	Beta (255,41)	Beta (256,54)	Beta (225,34)	Beta (224,9)	Beta (262,14)	Beta (267,22)

Table 5 : Cost-effectiveness analysis: Survival

Arm	Cost (€)	ΔC	Effectiveness (wks)	ΔE	ICER (€ / year)
Cap / Doc	5,466 [4,886;6,074]		81.9 [71.6;92.8]		
Pac	6,016 [5,328;6,710]	550 [223;877]	81.1 [64.6;93.4]	-0.8 [-21.4;16.8]	Dominated
Doc	6,917 [6,111;7,740]	1,451[962;1,922]	75.9 [59.7;96.6]	-5.9 [-26.4;18.0]	Dominated
Gem/Pac	11,052 [9,868;12,253]	5,586[4,894;6,290]	98.8 [88.9;109.0]	16.9 [2.1;31.3]	17,160

Figure 1 : Cost-Effectiveness Scatterplot

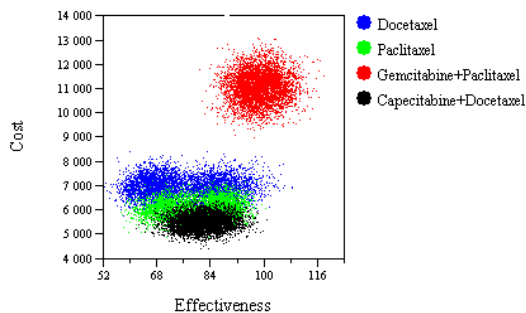


Figure 2 : ΔC and ΔE distributions (WTP = 959 €/week) : Pac vs Cap-Doc

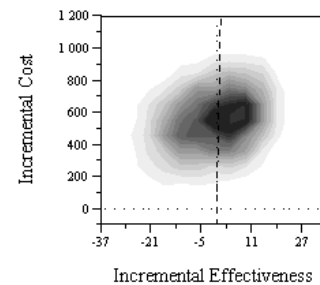


Figure 3 : ΔC and ΔE Distributions (WTP = 959 €/week) : Gem-Pac vs Cap-Doc

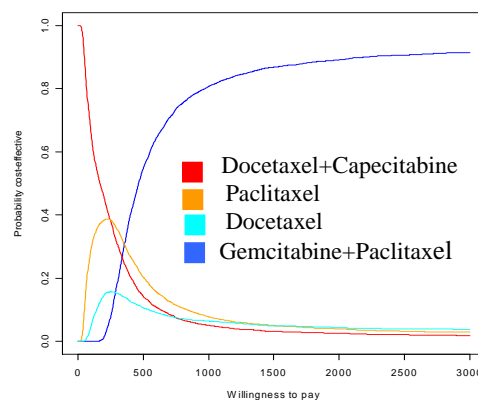
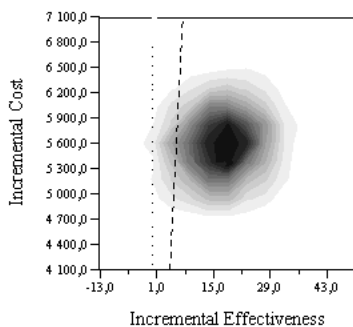


Figure 4 : Acceptability Curve : survival

Table 6 : Cost-effectiveness analysis: quality of life-adjusted survival

Arm	Cost (€)	ΔC	Effectiveness (wks)	ΔE	ICER (€ / year)
Cap / Doc	5,466 [4,886;6,074]		55.7 [49.3;62.5]		
Pac	6,015 [5,329;6,710]	550 [223;877]	56.6 [45.4;65.4]	0,9 [-12.8;12.7]	31,777
Doc	6,917 [6,111;7,740]	901[448;1,366]	53.8 [44.4;65.8]	-2.8 [-18.2;16.6]	Dominated
Gem / Pac	11,052 [9,869;12,253]	5,036 [4,427;5,652]	69.4 [63.1;75.9]	12.8 [1.4;26.3]	20,458
Cap / Doc	5,466 [4,886;6,074]		55.7 [49.3;62.5]		
Gem / Pac	11,052 [9,869;12,253]	5,586 [4,894;6,290]	69.4 [63.1;75.9]	13.7 [4.4;22.7]	21,202

Figure 5 : ΔC and ΔE distributions (WTP = 959 €/week) : Gem-Pac vs Cap-Doc

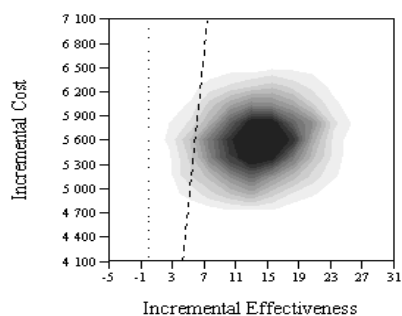


Figure 6 : Acceptability Curve : quality of life adjusted survival

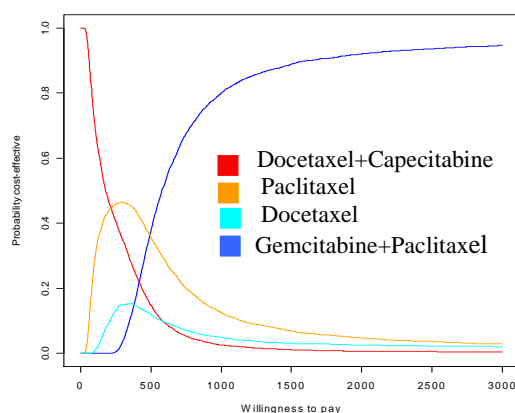


Table 7 : Cost-effectiveness analysis. HC for gemcitabine on D8

Arm	Cost (€)	ΔC	Effectiveness (wks)	ΔE	ICER (€ / year)
Cap / Doc	5,466 [4,886;6,074]		81.9 [71.6;92.8]		
Pac	6,016 [5,328;6,710]	550 [223;877]	81.1 [64.6;93.4]	-0.8 [-21.4;16.8]	Dominated
Doc	6,917 [6,111;7,740]	1451 [962;1922]	75.9 [59.7;96.6]	-5.9 [-26.4;18.0]	Dominated
Gem/Pac	10,205 [9,014;11,409]	4,740 [4,040;5,453]	98.8 [88.9;109.0]	16.9 [2.1;31.3]	14,585

References :

1. INSEE Résultats, La situation démographique en 2001. Mouvements de population. Espie M. Presse Med 1998 Sep 12 ;27(26) :1332-5.
2. Lerzo GL. Gemcitabine in metastatic breast cancer patients previously treated with anthracyclines and taxanes. Evaluation of response toxicity. Eur J Cancer 2002;38(SUPPL.3):S74.
3. Blackstein M. Gemcitabine as first-line therapy in patients with metastatic breast cancer : a phase II trial. Oncology 62(1), 2-8. 2002.
4. Spielmann M. Single-agent gemcitabine is active in previously treated metastatic breast cancer. Oncology 60(4), 303-307. 2001.
5. Schmid P. Phase II trial of gemcitabine as prolonged infusion in metastatic breast cancer. Anti-Cancer drugs 10(7), 625-631. 1999.
6. Perez-Manga G. Gemcitabine in combination with doxorubicin in advanced breast cancer : final results of a phase II pharmacokinetic trial. Journal of Clinical Oncology 18(13), 2545-2552. 2000.
7. Moiseyenko V. Phase II study of the combination of gemcitabine and cisplatin in anthracycline-resistant breast cancer patients. International Journal of Cancer, Supplement 2002;(13):196.
8. Stemmler 2000, Galvez 2000, Burch 2000 , Schroeder 2000, Nagourney 2000 99 98 97, Chaudhry 2000, Doroshow 2000
9. Fuentes H. Gemcitabine plus cisplatin is a highly active regimen in first-line treatment of metastatic breast cancer : results of a multicenter phase II trial.
10. Sanal SM. Gemcitabine and vinorelbine combination in patients with metastatic breast cancer. Breast Journal 8(3), 171-176. 2002.
11. Silva A. Neoadjuvant gemcitabine plus epirubicin in locally advanced breast cancer : evidence of activity in a phase II study. Prog./Proc. ASCO, 38th annual meeting, Orlando, Fl, May 18-21, 2002.
12. Murad AM. Phase II trial of the use of paclitaxel and gemcitabine as a salvage treatment in metastatic breast cancer. American Journal of Clinical Oncology :cancer clinical trials 24(3), 264-268. 2001.
13. Lenz F. A Phase II study of first-line combination chemotherapy with docetaxel and gemcitabine in anthracycline-pretreated, HER2-negative, metastatic breast cancer. Annals of Oncology 13(Suppl.5) : p53, 2002.
14. Launois R, Reboul-Marty J., Bonnetterre J et al. Evaluation médico-économique de la chimiothérapie de deuxième ligne dans le cancer du sein métastatique : comparaison du docétaxel, du paclitaxel et de la vinorelbine. Bulletin du Cancer. 1997; 84 (7) : 709-21.
15. Etude JHQG. Phase III Randomized Study of Paclitaxel With or Without Gemcitabine in Women With Unresectable, Locally Recurrent, or Metastatic Breast Cancer. Résultats intermédiaires, 2003.

16. Ravdin, Phase III comparison of docetaxel and paclitaxel in patients with metastatic breast cancer, ECCO 2003, abstract 670.
17. O'Shaughnessy J et al., Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer : phase III trial results, *Journal of Clinical Oncology*, Vol 20, N°12 2002: pp 2812-2823.
18. Albain KS. Global phase III study of gemcitabine plus paclitaxel vs. paclitaxel as frontline therapy for metastatic breast cancer : first report of overall survival. *American Society of Clinical Oncology Meeting proceedings*, Vol 23, 2004.
19. Moinpour C. Gemcitabine plus paclitaxel vs. paclitaxel as first-line treatment for anthracycline pre-treated metastatic breast cancer : quality of life and pain palliation results from the global phase III study. *American Society of Clinical Oncology Meeting proceedings*, Vol 23, 2004.
20. Collège des Economistes de la Santé. "Guide méthodologique pour l'évaluation économique des stratégies de santé". Juillet 2003
21. Weinstein MC., Siegel JE., Gold MR., Kamlet MS., Russel LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996 Oct 16;276(15):1553-8.
22. Sonneberg FA., Beck JR. Markov Models in Medical Decision Making : A practical guide. *Medical Decision Making* 1993 ; 13 ; 322-338.
23. Launois R., Croutsche JJ., Mégnighêto AC., Le Lay K. " L'apport indispensable de l'épidémiologie clinique aux modèles de Markov". *Journal d'Economie Médicale*, 1999, 17(5) : 343-361.
24. Miller DK., Homan SM. Determining transition probabilities : confusion and suggestions. *Medical Decision Making* 1994 ; 14 : 52-58.
25. Beck RJ., Pauker SG., Gottlieb JE., Klein K., Kassirer JP. A convenient Approximation of Life Expectancy (The DEALE). *The American Journal of Medicine*. 1982 ; 73 ; 889-897.
26. National Institute for Clinical Excellence. Technical guidance for manufacturers and sponsors on making a submission to a technology appraisal. Mars 2001.
27. Launois R. Un coût, des coûts, quels coûts ? *Journal d'Economie Médicale* 1999, T. 17, N° 1.
28. Ministère de l'emploi et de la solidarité. Hôpital 2007 : La mission « tarification à l'activité ». <http://www.sante.gouv.fr/htm/dossiers/t2a/1t2a.htm>
29. Agence Technique de l'Information sur l'Hospitalisation (ATIH/CTIP). Les tarifs de Groupes Homogènes de Séjour. 1^{er} Mars 2005. <http://www.le-pmsi.org/index.html>.
30. Arrêté du 31 décembre 2004 relatif au recueil et au traitement des données d'activité médicale des établissements de santé publics ou privés ayant une activité d'hospitalisation à domicile et à la transmission d'informations issues de ce traitement. Avis publié au *Journal Officiel*. 14 Janvier 2005.
31. Foulquier JN., Laugier A., Touboul E., Viardot JP., Schwartz LH. Coût de la chimiothérapie et coût du transport. *Bull. Cancer Radiother*. 1996 ; 83 : 170-171.

32. Direction des Affaires Economiques et Relations institutionnelles. LEEM. Circulaire N°5-0001. Liste T2A : Première liste de tarifs de responsabilité. Avis publié au Journal Officiel.
33. Arrêté du 17 décembre 2004 fixant la liste prévue à l'article L. 5126-4 du code de la santé publique. Avis publié au Journal Officiel. 26 décembre 2004.
34. Association pour le Développement de l'Internet en Pharmacie Hospitalière (ADIPH). Fiche explicative sur les prix de cession. <http://www.adiph.org/>
35. Arrêté du 20 décembre 2004 fixant les conditions d'utilisation des anticancéreux injectables inscrits sur la liste prévue à l'article L. 5126-4 du code de la santé publique. Avis publié au Journal Officiel. 23 décembre 2004.
36. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000, Vol. 17, N°5 : 479-500.
37. Claxton K, Sculpher M, McCabe C et al. Probabilistic analysis for NICE technology assessment : not an optional extra. *Health economics* 2005, 14 : 339-347.
38. Fenwick E., O'Brien B. Briggs A. Cost-effectiveness acceptability curves – facts, fallacies, and frequently asked questions. *Health Economics* 2004, 13 : 405-415.
39. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 2004;23:3105-3124.
40. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *British Medical Journal* 2003;328:472.
41. Lim E, Ali Z, Ali A, Routledge T, Edmonds L, Altman DG, Large S. Indirect comparison meta-analysis of aspirin therapy after coronary surgery. *British Medical Journal* 2003;327:1309.