Two Strategies for Managing Invasive Aspergillosis: A Decision Analysis


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We devised a diagnostic approach based on screening plasma for an Aspergillus antigen with use of a sandwich enzyme-linked immunosorbent assay (ELISA), thoracic computed tomographic scanning, and radionuclide imaging for managing patients at risk for invasive aspergillosis. We used a decision analytic model to compare this alternative strategy with the conventional strategy, which relies only on the presence of clinical symptoms, persistent fever, and chest roentgenographic findings.

Invasive pulmonary aspergillosis is a life-threatening complication of intensive chemotherapy for malignancies, chronic treatment with high dose corticosteroids, transplantation, and AIDS. Treating this infection as early as possible is one of the prerequisites for a favorable outcome [1], but since no reliable means of early diagnosis exists, it has become commonplace to treat patients at high risk empirically with amphotericin B when there is the slightest clinical suspicion of invasive aspergillosis [2]. As many as 68% of neutropenic patients will receive amphotericin B empirically, often for persistent fever alone [3, 4], even though the desoxycholate formulation of amphotericin B (DC-AmB; Fungizone, Bristol Myers Squibb, Woerden, the Netherlands) is associated with adverse drug reactions such as fever, rigors, and impaired renal function. In addition, the incidence of disease for most groups at risk is ≤10%. Therefore, alternative strategies are needed for the early recognition of invasive aspergillosis to allow better selection of patients who need treatment, while reducing the number of patients who are exposed unnecessarily to these drugs and their side effects.

In addition, better selection of patients who require treatment for invasive aspergillosis will also help to contain the cost of treatment when novel and expensive drugs are used. For instance, lipid formulations of amphotericin B, such as liposomal amphotericin B (L-AmB; Ambisome, Nexstar, St. Odilienberg, the Netherlands), amphotericin B lipid-complex (Abelcet, The Liposome Company, Reeuwijk, the Netherlands), and amphotericin B colloid dispersion (Amphocil, Zeneca Farma, Ridderkers, the Netherlands), are available and are being used increasingly for treating invasive aspergillosis because they induce fewer side effects than occur with the same dose of DC-AmB. Although equal or improved efficacy of lipid formulations of amphotericin B in treating invasive aspergillosis has not been proven, all the studies to date have shown that lipid formulations of amphotericin B are at least as effective as DC-AmB, even in those patients who did not respond [5–7]. Moreover, clinical trials are ongoing to establish the efficacy of lipid formulations of amphotericin B as empirical therapy for fever and neutropenia and as first-line therapy for documented aspergillosis [5].

However, the cost of treatment with these formulations is high. L-AmB is as much as 40 times more expensive than DC-AmB and is only considered for managing invasive aspergillosis in patients with impaired renal function or in those who are intolerant of DC-AmB or for managing progressive disease despite treatment with the desoxycholate formulation of the polyene [5]. Even if desirable, empirical treatment with L-AmB is simply not feasible since resources for health care are finite and there is increasing pressure to contain costs despite an inexorable rise in demand.

To address this issue we devised a diagnostic approach (alternative strategy) that incorporates Aspergillus antigen detection, high resolution CT scanning, and radionuclide imaging with indium-111-labeled human IgG ($^{111}$In-IgG). Each of these procedures have been shown to contribute to establishing the diagnosis of invasive aspergillosis, but the diagnostic value of an approach in which the tests and procedures are combined is unknown. The Aspergillus antigen galactomannan can be detected in plasma or serum samples from patients with invasive aspergillosis by using a commercially available sandwich ELISA (Platelia Aspergillus, Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France) [8]. This assay has been found to possess a sensitivity of 67%–100% and a specificity of...
81%–98.7% when performed with sera from patients receiving treatment for hematologic malignancies [9–13]. The sandwich ELISA becomes positive at an early stage of infection, and galactomannan has been detected in the sera of some patients even before signs and symptoms consistent with invasive aspergillosis became apparent [10]. Furthermore, ELISA results are available within 4 hours of collecting the sample [8]. Thoracic CT scanning is a major tool for the diagnosis of invasive aspergillosis in neutropenic patients, and the presence of a halo sign or an air-crescent sign is highly indicative of disease [14]. Recently, it was confirmed that the detection of halo signs in neutropenic patients is an early indicator of the presence of invasive aspergillosis [15]. However, the diagnostic sensitivity of a CT scan depends largely on tissue attenuation and an inflammatory response following fungal invasion, so the impaired inflammatory responses of immunocompromised patients may render the interpretation of the results of this technique more difficult than it is when patients are immunocompetent [16].

Radionuclide imaging with 111In-labeled human IgG is both sensitive and specific for detecting microbial invasion, even in the presence of a blunted inflammatory response, since accumulation of 111In-IgG is a result of capillary leakiness [16]. This technique has been successfully used to detect Aspergillus fumigatus infection in granulocytopenic patients [17] and may also be helpful in detecting nonrespiratory fungal lesions such as those in the sinuses or gut [16].

It is expected that by combining these diagnostic tests and procedures, candidates for treatment will be better selected than they are when the more permissive conventional strategy, which relies solely on the presence of persistent fever that is refractory to antibacterial agents and on the presence of pulmonary infiltrates on the chest roentgenogram, is used. However, since the costs incurred by the alternative diagnostic work-up will be higher, we decided to see whether these costs might be offset by savings made in the overall cost of treatment.

We used decision analysis, a modeling instrument for specifying complex choices in the face of uncertainty, to construct a model for comparing the number of patients expected to receive a diagnosis of invasive aspergillosis and to receive treatment according to each strategy. The expected costs of diagnosis and treatment with DC-AmB were calculated, and the impact of using L-AmB as first-line treatment in at least some cases of probable invasive aspergillosis was assessed. Finally, sensitivity analyses were performed to assess the impact of the necessary assumptions and impact of the estimates of certain variables on the robustness of the conclusions by varying one of the variables in the model while holding the other variables at their baseline value [18].

Materials and Methods

Diagnostic work-up. Presently in our Hematology Department at the University Hospital Nijmegen, invasive pulmonary aspergillosis is considered a possible diagnosis in neutropenic patients when fever persists for at least 5 days despite treatment with broad-spectrum antibacterial agents and when pulmonary infiltrates are apparent on the chest roentgenogram. Bronchial-lavage is then performed, and treatment is started empirically. Additional chest roentgenograms and culture results are used to determine the level of suspicion of invasive aspergillosis (conventional strategy, figure 1). The alternative diagnostic work-up involves prospective twice-weekly screening of serum or plasma for galactomannan in neutropenic patients receiving treatment for a hematologic malignancy during their stay in the hospital. When galactomannan is detected for the first time, a second sample is obtained for confirmation and, if the antigen is detected again, a high-resolution CT scan of the thorax and sinuses is obtained. If nothing is seen, 111In-IgG scintigraphy is performed.

A diagnosis of invasive aspergillosis will be presumed if antigen is detected and either imaging technique confirms the presence of a pulmonary infiltrate, sinusitis, or another sign of inflammation consistent with invasive aspergillosis. Antifungal treatment will then be started preemptively (alternative strategy, figure 1) [19]. Since patients may still develop invasive disease despite a negative ELISA result, a high-resolution CT scan will be obtained whenever there are grounds for suspecting invasive aspergillosis.

Empirical and preemptive treatment. Currently, 24% of our neutropenic patients receive DC-AmB empirically; 18% of these patients receive the drug for an average of 21 days for treatment of possible invasive aspergillosis, whereas the actual prevalence rate of this disease among patients admitted to the Hematology Department is estimated to be 6%. Since the average course of treatment is 35 days for these patients, we chose this figure to set the duration of preemptive treatment for patients whose infections were diagnosed by using the alternative strategy. However, we assumed that patients would receive only a 21-day course of treatment if the diagnosis of Invasive aspergillosis was shown to be unlikely later during the course of treatment.

The probabilities used in the decision analysis were based on our own data and those from the literature (table 1). We relied on estimates of the performance characteristics of CT scanning and 111In-IgG scintigraphy published for unselected neutropenic patients, since neither estimate is known for those in whom galactomannan is detected. The costs of diagnosis and treatment with use of both strategies were derived from hospital tariffs, for which diagnostic materials, depreciation costs of medical equipment, administration services, and consultation fees are taken into account (table 2). Treatment costs of both the desoxycorticosterone and lipid formulations of amphotericin B were based on their retail prices, assuming a 70-kg man was given 1 mg/(kg·d) of DC-AmB or 3 mg/(kg·d) of L-AmB, and were estimated to total $27 per day and $1,115 per day, respectively. No additional costs accruing to toxicity were taken into account because there were no accurate estimates available.

Decision analysis. The conventional and alternative strategies were defined, and baseline values of the probabilities of
each test result, together with the costs of the diagnostic tests and treatments, were estimated and incorporated into the decision tree by using the software program DATA version 2.6 (TreeAge Software, Williamstown, MA). After the path probabilities of each branch of the tree and the expected costs of diagnosis and treatment per patient were calculated for each strategy, sensitivity analysis was performed.

Primary calculations on the costs of both strategies were based on treatment with DC-AmB to determine whether the additional costs of the diagnostic tests included in the alternative strategy were outweighed by any savings resulting from the avoidance of unnecessary treatment. Since different values for both sensitivity and specificity of the sandwich ELISA have been reported [9–13], the impact of varying the performance characteristics of the sandwich ELISA on the positive and negative predictive values and the expected costs of the alternative strategy was determined by varying the sensitivity and specificity with use of values from the literature and the hypothetical values of 50% and 99%, given a 6% prevalence rate of infection. Besides this, we used the variables prevalence of infection (baseline value, 6%), the probability that a patient would receive empirical treatment with DC-AmB (baseline value, 6%), the probability that a patient would receive empirical treatment with L-AmB (baseline value, 24%), and the costs of the sandwich ELISA (baseline value, $10) in the sensitivity analysis.

Treatment with L-AmB. The impact of the availability of L-AmB was evaluated by incorporating three different possibilities of using this expensive drug in the model. First, we assumed that all patients with invasive aspergillosis diagnosed by the alternative strategy would be treated with L-AmB and that all patients whose cases were diagnosed by the conventional strategy would be treated with DC-AmB. Second, we analyzed the situation in which all patients with invasive aspergillosis diagnosed by the alternative strategy would be treated with L-AmB and that a varying proportion of those cases diagnosed by the conventional strategy would also be treated with

### Table 1. Baseline values and ranges of variables and test characteristics used to construct the decision tree for comparing two strategies for managing invasive aspergillosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Variable</th>
<th>Baseline value (%)</th>
</tr>
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<tbody>
<tr>
<td>[PR]</td>
<td>Prevalence of invasive aspergillosis</td>
<td>6</td>
</tr>
<tr>
<td>[10]</td>
<td>ELISA sensitivity</td>
<td>100</td>
</tr>
<tr>
<td>[10]</td>
<td>ELISA specificity</td>
<td>94</td>
</tr>
<tr>
<td>[14]</td>
<td>CT scan sensitivity</td>
<td>89</td>
</tr>
<tr>
<td>Set</td>
<td>CT scan specificity</td>
<td>95</td>
</tr>
<tr>
<td>[17]</td>
<td>111In-labeled IgG scintigraphy sensitivity</td>
<td>90</td>
</tr>
<tr>
<td>Set</td>
<td>111In-labeled IgG scintigraphy specificity</td>
<td>90</td>
</tr>
<tr>
<td>[PR]</td>
<td>Patients receiving empirical treatment with desoxycholate formulation of amphotericin B</td>
<td>24</td>
</tr>
</tbody>
</table>

**NOTE.** Set = estimates of performance characteristics.
L-AmB. Last, we assumed that the same proportion of patients whose cases were diagnosed according to both strategies would receive L-AmB. In addition, for the second and third scenarios, we calculated the threshold at which the expected costs were equal for both strategies. We also performed a two-way sensitivity analysis to examine the relationship between the proportion of patients treated with L-AmB and the prevalence of invasive aspergillosis.

Results

Probability of receiving treatment. The probability of receiving antifungal treatment as a result of the conventional strategy was .24 (figure 1; path probabilities, .06 + .18), while the probability of receiving antifungal treatment unnecessarily was .18. The probability of receiving antifungal treatment as a result of the alternative strategy was .073 (figure 1; path probabilities, .054 + .005 + .003 + .003 + .008 + .000), with 74% of these cases identified by antigen detection and confirmed by CT scanning. The probability of a patient incorrectly receiving treatment was .013, whereas only one of every 1,000 patients would incorrectly not receive treatment as a result of a positive ELISA result unconfirmed by imaging. The expected costs of diagnosis by the conventional and alternative strategies were estimated respectively to be $167 per patient and $463 per patient, respectively. Thus, the calculated savings on therapy of $93 per patient, accrued by using the alternative strategy, did not compensate for the extra investment in the diagnostic tests and procedures ($296 per patient). Under baseline assumptions, an overall investment of $203 per patient would be required to implement the alternative strategy.

Test characteristics. As expected, the positive predictive value for the conventional strategy was low (25%), and the negative predictive value was high (100%). Irrespective of the level of sensitivity, the positive predictive value of the alternative strategy declined from 88% to 54% as the specificity of the ELISA decreased, but the negative predictive value remained high (table 3). Decreasing the specificity of the test from 99% to 50% nearly doubled the expected costs per patient because the number of false-positive results increased, leading to the more frequent performance of CT scanning. By contrast, lowering the sensitivity of the ELISA from 99% to 50% had only a marginal effect on the expected costs per patient, reducing them from $480 per patient to $476 per patient when the specificity was 99%, and from $922 per patient to $919 per patient when the specificity was 50%. This effect is due to the fact that patients with a false diagnosis of freedom from disease will ultimately develop clinical signs and symptoms consistent with invasive aspergillosis and will still undergo CT scanning.

Sensitivity analyses. When the baseline values for the sensitivity and specificity of the sandwich ELISA were used, the alternative strategy became less expensive than the conventional strategy once the prevalence of invasive aspergillosis exceeded 13% (figure 2), and even when the worst test performance values were used, this threshold increased only slightly to 15.1%. Similarly, the threshold dropped only marginally to a prevalence of 11.5% when the best test performance values of sensitivity and specificity of the sandwich ELISA were used. At a prevalence rate of 13%, the probability of patients having invasive aspergillosis but wrongly not receiving treatment remained at approximately one in 1,000. Given baseline values for the performance of the alternative strategy, the conventional strategy became more expensive than the alternative strategy when the likelihood that a patient would be treated with DC-AmB exceeded 48.8%. The expected costs per patient of the two strategies were equal when the cost of the sandwich ELISA was $3.30.

Treatment with L-AmB. The expected costs of the alternative strategy were estimated to be $3,096 per patient, assuming that each patient with probable invasive aspergillosis was treated with L-AmB. This approach was always more expensive than the conventional strategy and treatment with DC-AmB, since thresholds could not be identified for the prevalence of infection, for the probability that a patient would receive empirical treatment, or for the costs of the sandwich ELISA. However, if L-AmB was available to all patients,
43.3% of the 24% of patients given empirical antifungal therapy as a result of the conventional strategy could be treated with this formulation before the alternative strategy became less expensive. Assuming that only a proportion of patients were treated with L-AmB, irrespective of the diagnostic strategy used, the one-way sensitivity analysis showed that the expected costs of the alternative strategy were only lower than those of the conventional strategy when >5.3% of all patients given antifungal therapy were treated with L-AmB. The two-way sensitivity analysis (figure 3) showed an inverse relationship between the proportion of patients treated with L-AmB for invasive aspergillosis and the prevalence of invasive aspergillosis.

Discussion

The increasing incidence of invasive aspergillosis [20], the high morbidity and mortality associated with the infection, and the costs of treatment with novel antifungal agents underscore the need for alternative approaches to managing this disease. The decision tree we constructed can be used as a model to predict the outcome and expected costs of implementing strategies for diagnosing or treating invasive aspergillosis in patients with hematologic malignancies. We chose the proportion of patients who would receive antifungal treatment, rather than survival, as the measure of outcome since the former variable is more commonplace and useful, whereas the mortality associated with invasive aspergillosis depends not only on antifungal treatment but also on whether remission from the underlying disease is achieved [1]. However, we acknowledge that the baseline values necessary for decision analysis are likely to differ between different institutions and depend on the nature and type of tests and procedures used to diagnose invasive aspergillosis, the prevalence of the disease, and, more important, the guidelines governing the institution of empirical antifungal therapy.

Under the assumed baseline values obtained at our hospital, the probability of receiving treatment unnecessarily could be reduced ~14-fold from .18 to .013 by using the alternative strategy we propose. We were also encouraged by the finding that the probability of withholding treatment incorrectly was likely to be very low (.001), although not zero. However, we assumed that no cases would go undiagnosed by the conventional strategy, which is unlikely to be the case, since invasive aspergillosis only becomes apparent at autopsy for the majority of patients [20].

The strategy we propose requires physicians to withhold treatment from patients who would otherwise have received therapy empirically. Typically, these patients would be febrile and neutropenic, but galactomannan would not be detected in blood samples, and CT scans would not show lesions consistent with invasive aspergillosis. Of course, other fungal pathogens may cause clinical signs and symptoms that are difficult to differentiate from invasive aspergillosis; nevertheless, the fear that patients may die of invasive aspergillosis compels many physicians to begin treatment empirically after 3–5 days of persistent fever that is refractory to antibacterial therapy, even in the absence of any pulmonary or sinus abnormalities. Thus, as many as two-thirds of all neutropenic patients are given empirical antifungal therapy [3, 4].

Clearly, the withholding of treatment will be difficult to achieve in such circumstances because the morbidity associated with DC-AmB therapy is regarded as less harmful than is the withholding of treatment from a patient with disease. Furthermore, when other less toxic antifungal agents are made available, the threshold for treating patients empirically will be lower still, with only the high cost of novel antifungal agents and the finiteness of resources providing disincentives to using these drugs empirically. The evaluation of alternative strategies for managing invasive aspergillosis is therefore imperative if we are to define the place of new antifungal agents and control their use.

The baseline values for the performance of the sandwich ELISA were based on the results of a prospective study of children during treatment for a hematologic malignancy [10]. However, false-positive ELISA results have been reported to occur within 30 days after bone marrow transplantation [11].

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Table 3. Positive and negative predictive values and expected costs per patient of an alternative strategy for the management of invasive aspergillosis, calculated for varying values of the sensitivity and specificity of the sandwich ELISA.

<table>
<thead>
<tr>
<th>Source of data</th>
<th>Sensitivity of ELISA (%)</th>
<th>Specificity of ELISA (%)</th>
<th>PPV of the strategy (%)</th>
<th>NPV of the strategy (%)</th>
<th>Total expected costs per patient ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>[10]</td>
<td>100</td>
<td>94</td>
<td>81</td>
<td>99.9</td>
<td>525</td>
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<tr>
<td>[12]</td>
<td>100</td>
<td>89</td>
<td>77</td>
<td>99.9</td>
<td>571</td>
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<tr>
<td>[9]</td>
<td>90</td>
<td>84</td>
<td>73</td>
<td>99.9</td>
<td>615</td>
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<tr>
<td>Hypothetical values</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>99</td>
<td>99</td>
<td>88</td>
<td>99.9</td>
<td>480</td>
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<td>50</td>
<td>54</td>
<td>99.7</td>
<td>919</td>
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</tbody>
</table>

NOTE. NPV = negative predictive value; PPV = positive predictive value.
of treatment with this formulation even though they were expected to be high because a larger number of cases diagnosed by the conventional strategy would receive treatment. As a consequence, all calculated expected costs were a conservative estimate of the actual costs. Nevertheless, the alternative strategy we propose will become less expensive than the conventional strategy if >5.3% of the treated patients are treated with L-AmB and it will become even less expensive if it proves tenable in circumstances where the majority of patients with hematologic malignancies currently receive empirical antifungal treatment.

Moreover, the probability of invasive aspergillosis is also high among these patients, so those cases of invasive aspergillosis that are diagnosed by using the alternative strategy may benefit the most from being given first-line treatment with L-AmB. However, the costs of treating all such patients with L-AmB will be high; thus a comparative study of L-AmB and DC-AmB is still required to determine the feasibility of this approach and within 10 days after the administration of cytotoxic therapy [21]. In the latter study [21], antigen was detected intermittently in a series of serum samples from some patients who had no evidence of invasive aspergillosis, which necessarily lowers the specificity of the sandwich ELISA [21]. However, since sequential tests and procedures are used in the alternative strategy to diagnose invasive aspergillosis, the impact of a less sensitive and specific ELISA on the positive and negative predictive values of the strategy as a whole is likely to be negligible. Nevertheless, the total costs per patient will increase considerably, especially if the specificity proves low. In addition to better selection of patients for antifungal treatment, the use of the sandwich ELISA as a screening test for galactomannan may also allow for the diagnosis to be made at an early stage of infection, at least for some patients [7–9].

Under baseline assumptions, we found that the current conventional strategy was less expensive per patient than was the alternative strategy when patients were treated exclusively with DC-AmB. However, we omitted the costs related to toxicity

**Figure 2.** One-way sensitivity analysis of the decision tree to determine the effect of the prevalence of invasive aspergillosis on the expected costs per patient. The prevalence of aspergillosis is varied in the sensitivity analysis which results in lines indicating the expected costs of each strategy. Where the lines of the strategies intersect (prevalence of 13%, given baseline test performance), this intersection defines a threshold point. If the prevalence of invasive aspergillosis is below the threshold, the conventional strategy is optimal; if this prevalence is above the threshold, then the alternative strategy is optimal. Baseline values for the sensitivity and specificity of ELISA in the alternative strategy are 100% and 94%, respectively. The worst case values, 67% for sensitivity and 84% for specificity, result in a threshold of 11.5%; in the best case these values are both 100%, which results in a threshold of 15.1%. (— = conventional strategy; = alternative strategy, baseline test performance; = alternative strategy, worst test performance; = alternative strategy, best test performance).

**Figure 3.** Two-way sensitivity analysis of the decision tree to determine the effect of the prevalence of invasive aspergillosis and the percentage of treated patients who received liposomal amphotericin B (L-AmB) in both strategies according to the expected costs per patient. As in figure 2, the results for the worst-case and best-case values of sensitivity and specificity, as well as baseline values for sensitivity and specificity of ELISA, are given. The curves indicate the combinations of values for the prevalence of aspergillosis and percentage of patients treated with L-AmB for which the expected costs of the two strategies are equal. Any coordinate to the left of the curves favors the conventional strategy, whereas any coordinate to the right of the curves favors the alternative strategy. There is an inverse relationship between prevalence of aspergillosis and percentage of patients treated with L-AmB. Thus, with our current prevalence, we would only need to treat one of 20 treated patients with L-AmB, and the alternative strategy would begin to pay for itself (— = baseline test performance; = worst test performance; = best test performance).
approach by taking into account other important aspects such as outcome, adverse drug reactions, and costs.

In conclusion, we constructed a decision model to explore the feasibility of implementing an alternative strategy for diagnosing invasive aspergillosis in patients receiving treatment for hematologic malignancies. This model indicated that screening for galactomannan and using imaging techniques, as compared with the conventional strategy, will reduce the number of patients who require treatment and therefore may help to control the use of toxic or expensive antifungal agents. We are now planning to assess the feasibility and the cost-effectiveness of the alternative strategy in a prospective comparative trial in which patients with hematologic malignancies, who will become neutropenic following cytotoxic therapy, will be randomized on admission to one or the other strategy, and all the relevant effects and costs, including those related to toxicity, will be registered.

References