Poor prognosis nonseminomatous germ-cell tumours (NSGCTs): should chemotherapy doses be reduced at first cycle to prevent acute respiratory distress syndrome in patients with multiple lung metastases?

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Background: Patients with extensive lung metastases from nonseminomatous germ-cell tumours (NSGCTs) and dyspnoea at presentation are at high risk of acute respiratory distress syndrome (ARDS) and death within the first weeks after chemotherapy induction. This syndrome is linked to acute intra-alveolar haemorrhage related to early tumour necrosis, which in turn, can be complicated by pulmonary infection promoted by neutropenia. The management of these patients was modified at Institut Gustave Roussy in 1997 to try to avoid this complication.

Patients and methods: Data concerning all patients with lung metastases from NSGCT and dyspnoea or a partial pressure of oxygen ($pO_2$) $<$80 mmHg treated from 1980 to 2006 in our institution were collected. Patients were treated in a specialised intensive care unit. From 1980 to 1997, the first chemotherapy cycle consisted in a full-dose regimen. After 1997, a 3-day reduced induction regimen of EP (cisplatin 20 mg/m\textsuperscript{2}/day and etoposide 100 mg/m\textsuperscript{2}/day) was used, with bleomycin and two additional days of EP being postponed to day 15, with the regular BEP regimen being started at day 21.

Results: Twenty-five patients with poor-risk disseminated NSGCT according to the International Germ Cell Consensus Classification Group had extensive lung metastases plus dyspnoea at presentation ($n = 6$), a $pO_2$ $<$80 mmHg ($n = 2$), or both criteria ($n = 17$). Median human chorionic gonadotrophin was 200 000 UI (range 11–8 920 000), and 18 of 25 (72%) patients also had nonpulmonary visceral metastases. During the 1980–1997 period, 13 of 15 patients (87%) developed ARDS, 10 of whom died, and only 4 of 15 (27%) patients were long-term survivors. In contrast, during the 1997–2006 period, only 3 of 10 patients (30%) developed ARDS ($P = 0.01$), 2 of whom died, and 4 of 10 (40%) eventually survived.

Conclusion: Initial reduction of chemotherapy doses during the first cycle of chemotherapy for poor prognosis NSGCT with extensive lung metastases seems to prevent the risk of early death due to ARDS.

Key words: ARDS, chemotherapy, germ-cell tumours, nonseminoma

introduction

Germ-cell tumours (GCTs) are the most common type of cancer in young men and disseminated GCTs are highly curable with cisplatin-based chemotherapy followed by surgical resection of residual masses [1, 2].

Patient prognosis is currently assessed using the International Germ Cell Consensus Classification [3] with three identified prognostic groups (good-risk, intermediate-risk, and poor-risk categories) defined on the basis of primary tumour site, the presence of extrapulmonary visceral metastases, and serum tumour marker levels before chemotherapy. Allocating patients to the appropriate prognostic group is important to adapt the burden of chemotherapy [4–6].

In contrast to previous classifications, the International Germ Cell Consensus Classification Group does not take into account the presence and number of lung metastases to assess the prognosis of disseminated nonseminomatous germ-cell tumour (NSGCT) because this factor was not shown to be independent in the multivariate analysis originally carried out to generate this classification. However, among patients suffering from poor prognosis NSGCT, a subset rapidly experience respiratory failure and die early during the course of treatment. These patients have extensive lung metastases and in most cases very high serum human chorionic gonadotrophin (hCG) levels at presentation [7]. The mechanism of respiratory
failure is that of acute respiratory distress syndrome (ARDS) soon after induction chemotherapy, defined as acute severe hypoxia requiring mechanical ventilation and bilateral infiltrates [8]. This syndrome was identified in the early 1980s and was previously termed ‘very high-risk NSGCT’ [7–9] or the ‘choriocarcinoma syndrome’ [10]. The pathogenesis of this respiratory complication likely involves postchemotherapy massive intra-alveolar haemorrhage, early tumour necrosis, and subsequent superinfection promoted by neutropenia. It is associated with a high mortality rate, especially in patients requiring artificial ventilation [11].

In 1997 in our institution, the therapeutic management of these patients was changed in order to reduce the risk of ARDS and early death. This study retrospectively evaluates the clinical management of these patients and their outcomes, including the incidence of ARDS and death from ARDS over a 25-year period.

patients and methods

patients
Using a computerised database and a systematic chart review, we identified the records of all patients with NSGCT and multiple lung metastases treated at Institut Gustave Roussy from April 1982 to November 2006. Patients with extensive lung metastases plus dyspnoea at presentation, hypoxia [defined as a partial pressure of oxygen (pO$_2$) <80 mmHg], or both criteria were selected. Dyspnoea is a subjective perception of shortness of breath. Because the studied population represented young patients, the limit of pO$_2$ <80 mmHg was used as a cut-off to more objectively assess it. When the primary tumour was in the testis, an orchidectomy was initially carried out and the diagnosis was confirmed by histological analysis according to the World Health Organization classification of GCTs [1, 2]. The diagnosis of advanced NSGCT was also made without pathological evidence in exceptional cases: a male patient presenting with diffuse lung metastases and highly elevated levels of α-fetoprotein (AFP) and/or hCG.

clinical evaluation
Pretreatment evaluation included a complete physical examination, useful blood chemistries (blood urea nitrogen, creatinine level, creatinine clearance, electrolytes, magnesium, and hepatic enzymes), a complete blood count, serum lactic dehydrogenase, radioimmunological determination of serum hCG and AFP levels, and a chest X-ray. Specific investigations were also carried out including an abdominal ultrasound and a computed tomography scan of the brain, the chest, and the abdomen.

treatment
All but two patients (one in 1992 and one in 1996) were admitted to the intensive care unit before beginning chemotherapy. Before treatment, patients were fitted with an indwelling central i.v. catheter. From 1982 to 1997, the different protocols used included a modified vinblastine–actinomycin–cyclophosphamide–bleomycin–cisplatin (VAB-6) regimen [12]: vinblastine 4 mg/m$^2$/day, actinomycin 1 mg/m$^2$/day, cyclophosphamide 600 mg/m$^2$/day on day 1 and bleomycin 20 UI/day on days 1–3 in a continuous infusion ($n$ = 2 patients); the EP regimen: etoposide 100 mg/m$^2$/day on days 1 and 2, doxorubicin 45 mg/m$^2$/day on day 1 and 2, cisplatin 120 mg/m$^2$/day on day 3, vinblastine 3 mg/m$^2$/day on day 22 and 26, and bleomycin 30 UI/day on days 22 and 26 ($n$ = 2 patients); a modified VB regimen [14]: vinblastine 0.05 mg/m$^2$/day and cisplatin 20 mg/m$^2$/day, as a 5-day continuous infusion ($n$ = 1 patient); and a full-dose CISCA/VB regimen [15]: cyclophosphamide 500 mg/m$^2$/day on day 1 and 2, doxorubicin 45 mg/m$^2$/day on day 1 and 2, cisplatin 120 mg/m$^2$/day on day 3, vinblastine 3 mg/m$^2$/day on day 22 and 26, and bleomycin 30 UI/day on days 22 and 26 ($n$ = 2 patients).

Beginning in 1997, the chemotherapy regimen used was changed to reduce the risk of ARDS and early death: only reduced doses of EP were used for induction treatment, while bleomycin administration was delayed to approximately day 15 in four patients and omitted in six patients in cycle 1 (Figure 1). Prophylaxis against neutropenia by granulocyte colony-stimulating factor (G-CSF) was also discussed on a case-by-case basis.

statistical analysis
All variables and patient characteristics were analysed using the SPSS software. The incidence of ARDS before and after 1997 was compared using the Fischer’s exact test. Differences were considered statistically significant when $P <0.05$.

results

patient characteristics
A total of 25 men, with a median age of 30 years, had disseminated NSGCT with a high risk of ARDS due to extensive metastases at high risk of acute respiratory distress syndrome.

<table>
<thead>
<tr>
<th>3 days of EP:</th>
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<tr>
<td>- Cisplatin 20 mg/m$^2$/day</td>
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<td>- Etoposide 100 mg/m$^2$/day</td>
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<td>- G-CSF</td>
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Evaluation

Day 10-15 :
- start bleomycin 30 UI/day
- 2 remaining days of EP

Evaluation

Day 21 :
- Classic BEP

Figure 1. Proposed chemotherapy regimen in patients with lung metastases at high risk of acute respiratory distress syndrome.
lung metastases plus dyspnoea at presentation \((n = 6)\), hypoxia \((pO_2 < 80 \text{ mmHg})\) \((n = 2)\), or both criteria \((n = 17)\). Their main characteristics are summarised in Table 1. The incidence of nonpulmonary visceral metastases was not higher during the earlier 1980–1997 period: eight \((80\%)\) versus nine patients \((60\%)\) during the latter 1997–2006 period.

**treatment**

After 1997, 7 of 10 patients had received the planned modified regimen consisting of etoposide 100 mg/m²/day and cisplatin 20 mg/m²/day on days 1–3. One patient had received etoposide 100 mg/m²/day and cisplatin 20 mg/m²/day for only two consecutive days. Finally, one patient had received a methotrexate, cisplatin, and vinblastine regimen because this patient presented brain metastases. This patient died 8 days after the beginning of chemotherapy.

During this period, 4 of 10 patients had received bleomycin on day 8 and 15 and 5 patients had received the last 2 days of the EP regimen after 5 days.

Prophylaxis against neutropenia with G-CSF was used in four patients.

Additional chemotherapy had been administered 3 weeks after induction using the classic BEP regimen in 9 of 10 patients.

**incidence and management of ARDS**

Baseline characteristics concerning handling of patients in intensive care unit were previously reported and extensively detailed by Kirch et al. [11]. For the recent cohort of patients, only one patient had mechanical ventilation.

The incidence of ARDS was lower in patients treated after 1997 using a modified chemotherapy regimen: 3 of 10 \((30\%)\) compared with 13 of 15 \((87\%)\) patients treated before 1997 \((P = 0.004)\) (Table 2).

**outcome**

During the 1980–1997 period, 13 of 15 patients \((87\%)\) developed an ARDS, of whom 10 died, and only 4 of 15 \((27\%)\) patients were long-term survivors. In contrast, during the 1997–2006 period, only 3 of 10 patients \((30\%)\) developed an ARDS, of whom 2 died, and 4 of 10 \((40\%)\) eventually survived (Table 2). The incidence of ARDS is significantly different \((P = 0.01)\).

**Table 1.** Patient characteristics

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<thead>
<tr>
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<tr>
<td>Age, years</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>30</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Range</td>
<td>23–39</td>
<td>25–46</td>
<td>23–46</td>
</tr>
<tr>
<td>Serum hCG (UI/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>81 700</td>
<td>265 000</td>
<td>165 000</td>
</tr>
<tr>
<td>Range</td>
<td>50–8 920 000</td>
<td>11–960 000</td>
<td>11–8 920 000</td>
</tr>
<tr>
<td>Proportion for nonpulmonary visceral metastases, (n (%))</td>
<td>9 ((60))</td>
<td>8 ((80))</td>
<td>17 ((68))</td>
</tr>
</tbody>
</table>

hCG, human chorionic gonadotrophin.

**discussion**

Although this syndrome was described >20 years ago, there is currently no firm evidence-based recommendation for treating patients with disseminated NSGCT and a high risk of ARDS following induction chemotherapy [1, 2]. Considering the frustrating high mortality observed during the 1980s and the early 1990s in this population of young men with a chemosensitive and theoretically chemocurable cancer, we decided in 1997 to attempt to circumvent the risk of postchemotherapy massive intra-alveolar haemorrhage related to early tumour necrosis by systematically reducing front-line chemotherapy doses. G-CSF was also used to prevent the risk of pulmonary superinfection facilitated by neutropenia, while bleomycin was delayed or omitted for ~2 weeks to preclude any additional lung toxicity. Moreover, other factors such as use of G-CSF and improvements in supportive care may also have contributed to improve the prognosis for these patients.

To maintain adequate dose intensity as much as possible, the remaining two additional days of the EP protocol were administered, when clinically feasible, on day 15 after induction chemotherapy. A regular BEP regimen was then started on day 22, up to a total of four cycles including cycle 1. The results indicate that this strategy may help to reduce the incidence of ARDS and ARDS-related deaths, without compromising long-term outcome, with an apparently higher long-term survival rate. We acknowledge, however, that this result should be considered with caution given the likelihood of biases including the small number of patients \((25\ overall)\) and the nonrandomised design of this study. This setting with patients at high risk for ARDS is certainly rare (<1% of the recruitment of patients with GCT in our national tertiary centre), making it virtually impossible to conduct a large prospective trial testing a specific therapeutic approach, even in the context of a multicentre endeavour. Even if this syndrome has been repeatedly reported in the form of case reports [16–20] or mentioned as cases in larger trials of poor prognosis NSGCTs during the last 25 years [9, 21, 22], this is, to our knowledge, the first study to report >10 cases and using a prospective systematic strategy to manage these patients. Other strategies involving low-dose induction chemotherapy are currently being evaluated (BABY BOP ...).

Its incidence in patients with lung metastases from NSGCT is not clearly defined and may vary from country to country [23]. One characteristic of this syndrome is the specific occurrence of high hCG levels in patients. It is unlikely that hCG may play a direct role in its pathogenesis. This feature more likely points to the presence of a heavy burden of pulmonary disease containing choriocarcinoma, a NSGCT subtype well-recognised...

**Table 2.** Incidence of ARDS and outcome

<table>
<thead>
<tr>
<th></th>
<th>1980–1997 ((n = 15))</th>
<th>1997–2006 ((n = 10))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS, (n) ((%)</td>
<td>13/15 ((87))</td>
<td>3/10 ((30))</td>
<td>0.01</td>
</tr>
<tr>
<td>Death from ARDS</td>
<td>10/15 ((66))</td>
<td>2/10 ((20))</td>
<td>0.04</td>
</tr>
<tr>
<td>Long-term survivors</td>
<td>4/15 ((27))</td>
<td>4/10 ((40))</td>
<td></td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome.
for its major angiogenesis properties [24] and therefore for its bleeding potential.

The rarity and difficulty of managing patients with lung metastases from NSGCT and a high risk of early ARDS once again underscore the importance of referring these patients as early as possible (within 24 h if feasible) to highly experienced cancer treatment centres with a high intake, in order to optimise their chances of cure, as previously indicated in retrospective studies focussing on centre size [25] and as now recommended by the European Germ Cell Cancer Consensus group [1, 2].

references