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Super-high-risk germ-cell tumors: a clinical entity

Report of eleven cases

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Abstract Among patients suffering from nonseminomatous germ-cell tumor, with a poor prognosis, a subset underwent respiratory failure and died very early in the course of their treatment. Between 1982 and 1989, 11 out of 56 such patients (20%) died within the first 5 weeks of chemotherapy. The clinical, radiological, biological and infectious characteristics of these patients were analyzed. Nine patients had extensive pulmonary metastases and the 2 others presented a bulky mediastinal mass with pleural effusion. All patients experienced acute respiratory distress during chemotherapy and underwent mechanical ventilation. All patients were febrile, and septicemia was documented in 7 cases. WHO grade 4 and grade 1–2 renal toxicities occurred in 3 and 4 patients respectively. There was no tumor lysis syndrome. All patients died within 35 days from the start of therapy; 4 were autopsied. These 11 patients represent a clinical entity, having what we called super-high-risk germ cell tumors. Early death is related to pulmonary distress within the first 5 weeks of therapy. The origin of the pulmonary distress is multifactorial: bulky disease of the chest, infection, and interstitial fibrosis. Immediate full-dose standard chemotherapy in association with intensive supportive care is recommended in the management of these patients.

Key words Poor-prognosis germ-cell tumors · Respiratory distress · Bulky mediastinum Pulmonary metastases Supportive care

Introduction

Despite a dramatic improvement in results of the treatment of nonseminomatous germ-cell tumors by cisplatin-based chemotherapy [11], a group of patients still has a poor prognosis [2, 3, 8, 18]. Studies have defined prognostic factors for a favorable or unfavorable outcome [2, 3, 8, 18]. In the aforementioned group of patients with poor prognosis, the complete remission rate does not exceed 50%–70% nor does the actuarial survival exceed 40%–60% at 2 years [11]. In this high-risk group, a subset of patients seems to have short life expectancy and needs particular management. Such patients were described by authors at the M. D. Anderson Hospital [15] and their specific management is mentioned in some prospective trials [6, 22, 23]. The purpose of this study is to define the clinical, radiological and biological characteristics of these high-risk patients who underwent respiratory failure and eventually died. We have called them super-high-risk patients. We also propose guidelines for their management.

Patients and methods

Between April 1982 and February 1989, 130 previously untreated male patients with advanced-stage nonseminomatous germ-cell tumors (NSGCT) were treated at the Institut Gustave-Roussy.

These patients entered prospective trials currently under investigation in our institution at the time of their treatment. The results of these trials have been shown elsewhere [7, 9, 10]. Patients were classified into either a good-risk or a poor-risk group according to a prognostic model developed at our institute [8]. Fifty-six patients were in the poor-risk group, and 11 of these died during the first 5 weeks of chemotherapy. These 11 patients are the subject of the present study.

All histological specimens were reviewed by the same pathologist and classified according to the World Health Organization (WHO) classification of germ-cell tumors [20]. The clinical stage was reported according to the Royal Marsden Hospital staging system [18]. Pretreatment evaluation included a complete physical examination, useful blood chemistry (blood urea nitrogen, creatinine, creatinine clearance, electrolytes, magnesium, hepatic enzymes), a complete blood count, serum lactic dehydrogenase, radioimmunological determination of human chorionic gonadotropin and α-fetoprotein serum levels and a chest radiograph. Specific investigations were performed according to the metastatic sites of disease and clinical status of the patient: abdominal ultrasonography, computed tomography (CT) scanning the brain and of the abdomen, and intravenous pyelography.

All patients were directly admitted to the Intensive Care Unit. Before treatment, patients were fitted with an indwelling central intravenous catheter. All patients underwent mechanical ventilation shortly after the beginning of the chemotherapy. A positive end-expiratory pressure was used when the P_aO_2 was below 60 mm Hg (8 kPa) with a forced inspiratory O_2 value above 50%. Of the 11 patients, 8 had hemodynamic monitoring by a Swan-Ganz catheter. Hemodynamic studies were indicated in the event of the suspicion of cardiogenic acute pulmonary edema (2 patients), renal failure with sepsis (1 patient), or monitoring for high-volume infusions in patients with respiratory failure treated by cisplatin (5 patients). Arterial blood pressure management was checked by an intra-arterial catheter. In the event of acute renal failure, patients were submitted to hemodialysis. A daily follow-up of patients included repeated measurements of arterial blood gases hemodynamic constants, daily complete blood counts, blood chemistry, and chest X-rays, and recordings of clinical findings and of toxicity.

These 11 poor-risk patients with acute respiratory failure were treated by different chemotherapeutic regimens. Although the situation of each patient was different during the ongoing prospective trial, the schedule of chemotherapy was adapted to the individual clinico-biological status. The different protocols used were a modified vinblastine/actinomycin/cyclophosphamide/bleomycin/cisplatin regimen [4]: vinblastine 4 mg m^{-2} day^{-1}, actinomycin 1 mg m^{-2} day^{-1}, cyclophosphamide 600 mg m^{-2} day^{-1}, cisplatin 120 mg m^{-2} day^{-1} on day 1 and bleomycin 20 mg day on days 1–3 in continuous infusion in 2 patients (1 patient did not actually receive cisplatin); an etoposide/cisplatin regimen [5]: etoposide 10 mg m^{-2} day^{-1} and cisplatin 20 mg m^{-2} day^{-1} on days 1–5 in 2 patients; low-dose etoposide/cisplatin: cisplatin 30 mg m^{-2} day^{-1} and either etoposide 50 mg m^{-2} day^{-1} on days 1 and 2 (in 1 patient) or etoposide 100 mg m^{-2} day^{-1} on days 1 and 2 (in 3 patients); a full-dose bleomycin/vinblastine/etoposide/double-dose cisplatin regimen [10]: vinblastine 0.2 mg kg^{-1} day^{-1} on day 1 and etoposide 100 mg m^{-2} day^{-1}, cisplatin 40 mg m^{-2} day^{-1} and bleomycin 20 mg/day in continuous infusion during days 1–5 in 2 patients; a modified vinblastine/cisplatin regimen [16]: vinblastine 0.05 mg kg^{-1} day^{-1} and cisplatin 20 mg m^{-2} day^{-1}, both in 5 days continuous infusion in 1 patient.

Response and toxicity were assessed according to the World Health Organization (WHO) criteria [19]. The risk of death for these patients in the intensive-care unit was evaluable with the simplified acute physiology score [13]. Survival was measured from the initiation of the chemotherapy until the patient's death. An autopsy was performed in 4 patients.

Results

Patients characteristics are shown in Tables 1 and 2. Table 1 shows the characteristics of patients' tumors and Table 2 the main symptoms encountered by the patients. Details of each individual patient's treatment and progress are shown in Table 3.

Clinical evolution and tumor response to chemotherapy

All patients died within the first 5 weeks following the start of the chemotherapy. The overall clinical response was a stabilization of tumor size in virtually 11 patients (2 minor responses and 9 with stable disease according to WHO criteria). However, when seric tumor marker

Table 1 Characteristics of the germ-cell tumors. *AFP* α-fetoprotein, *HCG* human chorionic gonadotropin, *LDH* lactate dehydrogenase, *CC* choriocarcinoma, *H+* hepatic metastases, *CNS+* central nervous system metastases

Number of patients	11
Median age (range) (years)	27 (22–34)
Primary tumor	
Testis	4
Extragonadal	7
Clinical stage[a]	
III C	1
IV AL3	3
IV CL3 H+	5
IV CL3 CNS+	1
IV CL1 H+	1
Initial tumor markers	
AFP <10 ng/ml and elevated HCG	7
Range of HCG level (mIU/ml)	9114–1080000
HCG <10 mIU/ml and elevated AFP	1
Value of AFP level (ng/ml)	710000
HCG >10 mIU/ml and AFP >10 ng/ml	3
Range of HCG level (mIU/ml)	50–8920000
Range of AFP level (ng/ml)	460–11600
LDH level (UI/l)	
<1000	0
1000–2000	5
2000–3000	4
>3000	2
Probability of complete remission[b]	
Median	0.05
Range	0–0.40
Histology[c]	
Pure choriocarcinoma	6
Pure embryonal carcinoma	2
Teratocarcinoma with CC	2
Teratocarcinoma with yolk-sac tumor	1

[a] Royal Marsden Hospital staging system [18]
[b] Probability of complete remission according to Institut Gustave-Roussy prognostic mathematical model [8]
[c] World Health Organization classification [20]

Table 2 Non-tumoral patient characteristics. P_aO_2 Arterial O_2 pressure, S_aO_2 percentage O_2 saturation

Symptoms at presentation		
Chest pain		6
Hemoptysis		4
Dyspnea		9
Weight loss[a]		4
Initial performance status[b]		
0		0
1		4
2		6
3		1
Arterial blood gas (at atmospheric pressure)		
P_aO_2 (mmHg)	>60	2
	⩽60	9
S_aO_2 (%)	>90	6
	⩽90	5
White blood cells >10000/mm^3		9

[a] Weight loss greater than 10% of body weight
[b] World Health Organization criteria [19]

levels were measured during evolution (8 patients) we observed that 3 patients had a more than 50% tumor marker level decrease and 4 patients had an increase of tumor marker level. Four patients had an autopsy. The pathological findings were as follows: (a) tumoral involvement of different sites: lung 3 patients, lumbo-aortic lymph nodes 3 patients, mediastinum 2 patients, liver 2 patients, kidney 3 patients, thyroid 1 patient, gastro-intestinal tract 1 patient, pancreas 1 patient, adrenal gland 1 patient; (b) major sites of infection: lung 3 patients, renal excretory system (pyelonephritis) 1 patient, pleura 1 patient. (c) In all 4 cases burdens were necrotic and fibrotic but viable residual tumor was always observed. There was no mature teratoma. (d) Pulmonary interstitial fibrosis was observed twice and was mild in 1 patient and extensive in the other.

Respiratory function and radiological aspect of lungs

At the time of initial work-up there were two distinct radiological aspects. Eight patients had multiple nodules in the lung (more than 20% of a plain X-ray chest surface) which were associated with alveolar opacities in 3 patients and hilar adenopathies in 4. Figure 1 shows a typical radiograph of this kind of presentation. Three other patients had bulky mediastinal lymph nodes (more than 5 cm in diameter) with atelectasia and pleural effusion. Figure 2 shows the lung radiograph of such of a patient.

As the observation continued two major facts emerged: (a) in all patients there was an increase of alveolar abnormalities; (b) the objective response to chemotherapy in the lung was minor response in 4 patients, progression in 3 and stable disease in 4. At the time of the patient's death, the lungs were found to be "uniformly white" on the chest X-ray. Five patients experienced various positive-end-expiratory-pressure-related baro-traumatisms: pneumothorax in 2 patients, subcutaneous emphysema in 3, pneumomediastinitis in 1 and increase of vena cava compression in 1.

Hemodynamic studies

In all patients the pulmonary arterial wedge pressure was normal, the systemic vascular resistance was low (median 621 dynes m^{-2} cm^{-5}, range 336–1280) and the cardiac index increased (median 5.3 l min^{-1} m^{-2}, range 3.6–8.6).

Table 3 Treatment and outcome. *VC* Vena cava, *H* high-dose cisplatin (⩾100 mg/m^2), *L* low-dose cisplatin (<100 mg/m^2), *ND* not done, ↗ increasing seric level of tumor markers. Regimens of chemotherapy (see text): *EP* standard etoposide + cisplatin [5], *lEP* low-dose etoposide + cisplatin, *mVAB6* modified vinblastine + actinomycin + cyclophosphamide + bleomycin + cisplatin regimen [4], *T85* combination of bleomycin + vinblastine + etoposide + double-dose cisplatin [10]

Treatment and outcome	1	2	3	4	5	6	7	8	9	10	11
Obstructive uropathy	0	0	0	0	0	+	0	0	0	0	+
Renal involvement by tumor	+	0	+	0	0	+	0	0	0	0	0
Creatinine clearance (ml/mn)	72	37	5	77	103	84	88	123	176	102	127
VC compression	0	+	0	0	+	0	0	0	0	0	0
Regimen of chemotherapy	EP	mVAB6	mVAB6	T85	EP	T85	IEP	IEP	VB4	IEP	IEP
Dose cisplatin	H	H	O	H	H	H	L	L	L	L	L
Dose of bleomycin (mg)	0	100	80	140	0	200	0	0	0	0	0
Renal toxicity[a]	4	4	4	0	0	1	0	3	2	1	2
Neutropenia[a]	4	3	0	4	4	4	0	3	0	0	0
Hemocultures	+	+	0	+	+	0	+	+	0	+	0
Marker level decrease	>99%	ND	>50%	>99%	ND	ND	>50%	↗	↗	↗	↗
Survival (days)	35	30	28	22	13	12	10	9	7	6	6

[a] World Health Organization (WHO) criteria [19]

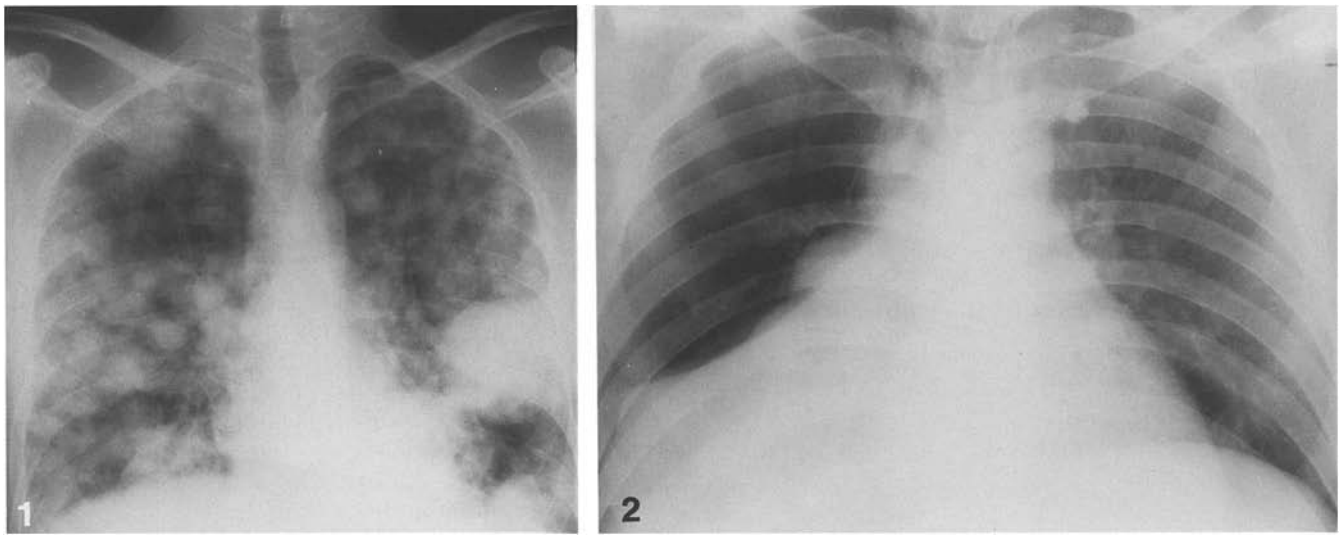

Fig. 1 Chest X-ray of a patient showing multiple nodules with alveolar opacities and hilar adenopathies

Fig. 2 Chest X-ray of a patient showing bulky mediastinal lymph nodes with pleural effusion

Renal function

WHO grade 4 renal toxicity occurred in 3 patients. They were subsequently submitted to extrarenal hemodialysis. In 1 of them the renal function returned to normal. Four patients had WHO grade 1–2 renal toxicity and 4 patients did not have any renal impairment. None of the patients had a lysis syndrome.

Hematological evolution

At presentation 9 patients had a hyperleukocytosis (white blood cells above 10000/mm^3). As observation continued, patients had WHO grade 4 neutropenia, which was reversible in 2 patients (within 7 and 8 days). Two patients died during the aplasic period. Transient WHO grade 3 neutropenia occurred in 2 patients and 5 patients did not experience any change in their white blood cells. Five patients had hyperleukocytosis at the time of their death. The platelet count was less than 3000/m^3 in 4 patients, in 2 of them platelet transfusion was required.

Infectious complications

All patients were febrile during the period of observation and received antibiotics.

Despite numerous blood cultures and bacteriological studies of urine, stools, pleural effusion, catheters and tubes, no specific localized infections were identified before death. However septicemia was documented in 7 patients: in 5 patients one micro-organism was identified (nonhemolytic *Streptococcus* 1, *Pseudomonas aeruginosa* 1, *Staphylococcus aureus* 2, *Staphylococcus epidermitis* 1), and in 2 patients some micro-organisms were concurrently present in the blood (*Ps. aeruginosa* + *Serratia marcessens* + *S. aureus* 1 patient, *Ps. aeruginosa* + *Hemophylus influenza* 1 patient).

In these 11 patients, 26 intra-arterial and intravenous catheters were placed. Six of them were contaminated when monitored by the Maki technique [17]. The same micro-organism (*S. aureus*) was found both in the indwelling material and in the blood in only 1 patient. The results of the antibiogram of the isolated micro-organisms were retrospectively compared to the activity spectrum of empiric antibiotics currently administered to the patients. In 5 patients the antibiotics were not active, and in 2 patients only one antibiotic demonstrated some activity.

Simplified acute physiology score (SAPS)

At presentation the mean SAPS was 10 (range 4–19).

Correlation between patients' characteristics, treatment, toxicity and progress

The data are summarized in Table 3. Survival seems to be correlated to the chemotherapy regimen, mainly to cisplatin dosage, and to the actual decrease of tumor marker level during the course of the observation. In fact, the first four patients in Table 3, who survived more than 20 days, received a higher dose of cisplatin and experienced a more impressive reduction of tumor markers than the other 7 patients who died within 15 days.

WHO grade 4 renal toxicity seems related to some anatomical or physiological disorders: pretreatment creatinine clearance impairment in 2 patients (37 ml/min and 72 ml/min), renal metastases in 2 patients and the hemodynamic consequence of vena cava compression in 1 patient. These factors could have cumulative effects.

The hematological toxicity correlated well with the dose intensity of the chemotherapy regimen, and not with renal impairment. However, mono- and polymicrobial septicemia occurred preferentially in neutropenic patients.

Discussion

The characteristics of patients with a dismal prognosis have not been yet extensively reported in clinical trials, apart from some case reports described in the literature [1, 15, 21]. The 11 patients studied in this paper are clearly a subgroup of poor-risk patients who experienced early death within the first 5 weeks of therapy. Super-high-risk patients represent, in our experience, 11/56 (20%) of poor-risk patients defined by our prognostic model [8]. Such a high frequency must be interpreted carefully, since a selection bias could be introduced by studying only patients collected in our referral center. They are characterized by respiratory distress, which is the major cause of death. Pulmonary distress is probably related to the bulk of lung metastases, to the pulmonary infection and finally to interstitial fibrosis. The origin of the latter may be multifactorial: oxygen-induced fibrosis, bleomycin-related fibrosis, or interstitial infection. No definite proof of the origin of pulmonary failure can be found from our observations, but we have established that it is not related to cardiac failure. It is noteworthy that there were no metabolic disorders related to tumor lysis syndrome in these patients. The lack of this phenomenon in germ-cell tumors of poor prognosis has been reported elsewhere [12].

Infection may be an associated cause of death in these patients; some data favor this hypothesis: (a) 6/7 isolated micro-organisms were found in blood cultures performed within the 3 days preceding the death of the patients. (b) The retrospective study of the antibiograms done for these isolated micro-organisms revealed that, in 5 patients, the antibiotics actually given were not active and, in 2 patients, only one antibiotic was active. (c) The 4 autopsied patients had profound septic sites. (d) Two patients were in aplasia and 5 had a hyperleukocytosis at the time of their death. (e) Eight patients had a hemodynamic profile of hyperkinetic status.

The clinical presentation of these patients is compatible with the so-called "choriocarcinoma syndrome" [15]. This syndrome is not only observed in pure choriocarcinoma but also in other embryonal tumors as reported in case 2 of Benditt et al. [1]. In our 11 patients hemoptysia was present in only 4; however, respiratory distress occurred in the whole patient population. Nevertheless, 3 among 5 patients with choriocarcinoma syndrome reported by Logothetis et al. survived [14]. Thus, we can conclude that super-high-risk germ-cell patients are somehow different from patients with choriocarcinoma syndrome.

Another similar clinical presentation was described by Phipps et al. and called pulmonary tumor lysis syndrome [24]. However, autopsies performed in 4 of our cases did not reveal extensive pulmonary necrosis and fibrosis as defined for this localized lysis damage.

In our experience, initial presentation characteristics of super-high-risk patients included three aspects. (a) These patients have of two or more of the following associated symptoms: dyspnea, chest pain, hemoptysia and weight loss. (b) The tumoral status of these patients is far advanced disease: 9 patients had bulky pulmonary disease (IV L3) of whom 5 had liver metastases, a very high level of human chorionic gonadotropin (HCG) (6 patients had HCG above 100000 mIU/ml). (c) The biological status of these patients is characterized by the presence of hypoxemia: P_aO_2 was less than 60 mm Hg (8 kPa) in 9 patients.

The clinical representation being the most important characteristic, it is concluded that the key to therapy is immediate treatment.

Although the optimal therapy of this subgroup remains to be defined, 5 of our patients who died within 2 weeks (patients 7, 8, 9, 10, 11) were submitted to a reduced dose of cisplatin-induction chemotherapy. Therefore, a standard dose of cisplatin-containing regimens is recommended. Moreover, bleomycin must be avoided since it may induce pulmonary fibrosis. However, bleomycin should be introduced again when tumor masses are debulked because its complete omission was demonstrated to be detremental in a prospective randomized trial [14].

As infection appears to be a potential adjuvant cause of death, and as profound septic sanctuaries are not found early, we recommend that potential sites of infection are investigated with the aim of treating them prophylactically before aplasia occurs. A CT scan of the thorax is recommended to detect alveolar infection, as it has been shown to be more effective in this setting than a plain chest X-ray [25]. Bronchoscopy with bronchio-alveolar washing and bronchial brushing may allow the isolation of adequate bacteriological samples. A CT scan and/or echography of the abdomen is recommended to detect the presence of a profound abdominal abcess. Routine blood cultures are also recommended, even in the absence of fever. The prescription of antibiogram-adapted antibiotics are mandatory at

the start of the chemotherapy. An option in the emergency setting is to treat patients with large prophylactic doses of broad-spectrum antibiotics including *Pseudomonas*-active antibiotics and penicillinase-resistant antibiotics.

Thus the combination of early careful chemotherapy and intensive supportive care may enhance the survival of this group of patients. Such patients often are ineligible for prospective trials. Their eventual inclusion in reports as early deaths is recommended when interpreting the results of clinical trials in patients with poor-risk nonseminomatous germ-cell tumors. So far, it is difficult to recommand a very aggressive approach in these patients who are actually treated palliatively. However, the age of patients and the high sensitivity of the tumor to chemotherapy may imply a curative approach based both on supportive care and carefully managed conventional chemotherapy.

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