Selenium status in the body and proliferative activity of malignant cells

Sir,

Avanzini and co-workers recently reported the results of their study on serum selenium concentrations in patients with newly diagnosed lymphoid malignancies. Interestingly, as compared to controls, selenium (Se) levels were significantly lower in patients with non-Hodgkin’s lymphoma (in a representative sample) in IV stage and/or in those with high grade disease. However, literature reports of serum Se levels in patients with lymphoid malignancy or solid tumors are discordant. These discrepancies may be due to case series that are not directly comparable among themselves or with healthy control cohorts.

It must be borne in mind that the elevated variability of serum Se may be due to factors other than cancer such as age, sex, body mass, dietary habits, life style (alcohol, smoking), intercurrent disease and medications.

When considering the various biological roles of Se (proliferation and differentiation of oncogenes by normal and malignant cells, carcinogen metabolism, cellular immune response, prevention of oxidative stress, apoptosis) and when addressing the topic of whether Se is a risk factor or a protection against cancer, one must evaluate selenium levels both in serum and in biological material, and to integrate selenium intake with its status in the body districts (blood, depots, healthy and diseased tissue) and we wish to point out one point to the wide spread of values in the series, the findings are not directly comparable among themselves or with healthy control cohorts.

Several factors may influence Se exchanges between labile pools, deposits and cancer tissue, and we wish to point out one important factor which has so far received little attention but which might influence selenium profiles, namely the proliferative activity of cancer cells. Of particular interest along this line of thought is the finding by Avanzini and co-workers of an inverse relationship between serum selenium and β2-microglobulin, an important index of the turnover of neoplastic cells.

In an ongoing study on Se levels in the serum and hair of women with breast cancer (unpublished data), we observed that patients recruited at an early clinical stage had lower serum Se and higher Se hair content with respect to patients at a more advanced stage or to healthy controls:

Stage 0-I (n=42): serum Se mean value 76.2±21.7 µg/L, hair Se content geometric mean 416.5 µg/g
Stage II-IV (n=44): serum Se mean value 81.5±22.4 µg/L, hair Se content geometric mean 335.2 µg/g

Controls (n=86): serum Se mean value 88.6±26.4 µg/L, hair Se content geometric mean 370.5 µg/g

Though our data fell short of statistical significance, due in part to the wide spread of values in the series, the findings are suggestive in light of the kinetic properties of tumor cells. Indeed the relationship between Se and cellular growth might influence selenium status is interesting and is partially supported by prior data, including our own. However, due to the limited evidence available on this topic, further data are needed to confirm that enhanced selenium uptake by neoplastic tissue may vary according to the mitotic activity of the cancer cells.

Piccinini and colleagues also addressed a fundamental issue in epidemiologic and clinical research on the health effects of selenium: the methodology for exposure assessment and, in particular, the use of biomarkers as surrogate measures of selenium exposure (represented in most individuals by dietary intake). Selenium content of serum, plasma, erythrocytes, whole blood, hair, toenails, and urine are among the biomarkers most frequently used in epidemiologic and clinical studies. Serum, plasma and urine selenium are short-term markers of exposure, whereas the remaining indicators tend to reflect long-term selenium intake. The limitations of these indicators as surrogate measures of intake have been reviewed. Selenium-dependent glutathione peroxidase activity has also been evaluated as a possible biomarker of exposure, but it does not appear to be a reliable indicator of selenium intake since the correlation between the two parameters is not linear and, what is more, glutathione peroxidase activity may be induced by oxidizing agents (including selenium itself).

In our clinical studies we evaluated selenium exposure through determination of serum selenium content, a sensitive short-term selenium marker, because we were interested in a possible relationship between the clinical characteristics of lymphoid malignancies and recent changes in selenium status. Obviously the characteristic that makes serum selenium content of interest in clinical research, i.e. its ability to reflect short-term selenium intake, also represents a limitation in an epidemiologic setting, particularly in retrospective studies where selenium status is likely to be affected by the disease, at least in some body tissues. This is why we did not consider our results to be contradictory to the prior hypothesis of a direct association between selenium exposure and the risk of lymphoid malignancies, though they did not add any evidence to support this hypothesis.

Biomarkers, however, may not adequately reflect selenium intake due to factors such as gender, body mass, medical

Selenium and lymphoid malignancies (Reply)

Sir,

Piccinini et al.’s hypothesis that the proliferative activity of malignant lymphoid cells and of cancer cells in general might influence selenium status is interesting and is partially supported by prior data, including our own. However, due to the limited evidence available on this topic, further data are needed to confirm that enhanced selenium uptake by neoplastic tissue may vary according to the mitotic activity of the cancer cells.

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Biomarkers, however, may not adequately reflect selenium intake due to factors such as gender, body mass, medical

References


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tionship between selenium and cancer, we agree with Piccinini et al. that selenium, should also be considered.5

metals, which can markedly influence the biological activity of selenium.5

intake or biomarkers – other factors such as exposure to heavy metals have suggested the usefulness of evaluating average selenium exposure through estimation of usual dietary intake, but unfortunately this methodology is also subject to limitations due to the high variability in the selenium content of foodstuffs in several geographical areas.11,13 The degree of correlation between selenium intake, as estimated through food diaries or other techniques, and biomarkers as surrogate measures of exposure has been found to be satisfactory in some studies but not in all.8,10

An important advantage to estimating dietary intake would be the possibility of determining the specific chemical forms of selenium to which the human body has been exposed before and in vivo in response to exposure. Whichever approach is adopted in the assessment of selenium exposure – dietary intake or biomarkers – other factors such as exposure to heavy metals, which can markedly influence the biological activity of selenium, should also be considered.11

Despite the complexity of epidemiologic studies on the relationship between selenium and cancer, we agree with Piccinini et al. on the need to investigate this issue further, especially in the light of the results of two recent studies that have analyzed the effect of selective long-term selenium exposure (self-administered or accidental) on cancer risk.7,11

References


When to perform peripheral blood progenitor cell collection in hematological patients?

Sir,

we read with interest the paper by Torretta et al. on the experience of Pavia University regarding circulating progenitor cell collection in cancer patients. The authors stated that, using daily flow cytometric monitoring of CD34+ cells in the peripheral blood (PB), collections were started when these cells reached a value of 20 µL. However, the possibility of harvesting even though circulating CD34+ cells were below 20 µL (between 10 and 20 µL) was always considered in relation to the particular clinical history, state of disease and therapeutic strategy adopted for each patient.

In agreement with this latter statement, we would like to describe our experience on this topic. As Torretta et al. reported, we usually start leukaphereses when white cells in the PB, evaluated in the morning just before collection, are greater than 1000 µL and CD34+ cells greater than 20 µL. However, when making clinical decisions, we have to consider that some patients, due to their clinical situation such as secondary myelodysplasia, exhausted marrow, previous chemo- or radiotherapy may have serious problems in mobilizing CD34+ progenitor cells in the blood.3,4 This leads to the need for a larger number of procedures to obtain the optimum yield of progenitor cells for a safe engraftment. In this setting, some authors suggest a threshold dose of 2×10^6/kg CD34+ cells, while others refer that less than 5×10^6/kg, although able to restore hematopoiesis in most cases, can be responsible for delayed engraftment or defective platelet reconstitution and recommend collecting not less than 8×10^6/kg CD34+ cells to ensure a rapid, complete and sustained hematopoietic recovery.3,4 We retrospectively analyzed our data on 54 patients suffering from hematological malignancies (21 multiple myelomas, 14 acute myeloid leukemias, 10 non-Hodgkin’s lymphomas, 9 Hodgkin’s disease) who received high-dose mobilizing chemotherapy plus growth factor administration (G-CSF and in some cases GM-CSF) at our Institution between April 1993 and July 1996. The total number of leukaphereses performed was 159 (mean number per patient 2.9, range 1-4). About 9 liters of blood were processed for each patient.

The amount of CD34+ cells collected at each leukapheresis was analyzed in relation to the number of CD34+ cells in the PB, in order to evaluate the predictive yield capacity of the latter. A

Figure 1. CD34+ progenitor cell content (x 10^6/kg) in leukaphereses in relation to the PB CD34+ cell concentration (/µL).
All-trans retinoic acid might also induce apoptosis in freshly isolated chronic myeloid leukemia cells

Sirs,

we read with interest the recent letters by Martinelli and coworkers1 and Zinzani and coworkers2 on the induction of apoptosis by the nucleoside analogs fludarabine (FAMP), 2-chlorodeoxyadenosine (2-CdA) and 2-deoxycytocinomycin (DFC), whether used alone or in combination with α-interferon (α-IFN), in freshly isolated leukemic cells from chronic myeloid leukemia (CML). Apoptotic cell death, as demonstrated by electrophoretic gel DNA fragmentation pattern, was induced by both FAMP and 2-CdA, either alone or in combination with α-IFN, whereas DCF, with or without α-IFN, failed to do so. The authors focused on the opportuneness of promoting further in vitro and in vivo studies with these two promising adenosine analogs, possibly employing assays able to measure programmed cell death. We agree with the authors about the timeliness of exploring new effective drugs capable of driving the CML clone into apoptosis, and on this point we would like to provide further evidence in support of their in vitro findings.

We recently tested the in vitro capability of FAMP and all-trans retinoic acid (ATRA) to drive peripheral myeloid cells from untreated Ph+ CML patients in chronic phase into apoptosis. Apoptosis was measured by using simple and reliable flow cytometric methods based on decreased forward light, increased right angle scatter and reduced propidium iodide fluorescence stainability.3 These methods, as compared to electrophoretic gel DNA fragmentation assays, which allow only bulk apoptosis measurement, are able to detect programmed cell death on a single cell basis. In our model, CML cells cultured alone in standard complete medium (RPMI 1640 plus 10% FCS) showed a low apoptotic cell rate (6.8% at 96 hours of culture) at all the different time points tested (24, 48, 72, 96 hours). By contrast, when cultures were performed in the presence of FAMP (5 μM) apoptosis reached 26.3% and 31.7% at 72 and 96 hours, respectively. Similar results were obtained when FAMP was substituted with ATRA (3 μM). This agent, which was previously shown to induce apoptosis in freshly isolated chronic promyelocytic leukemia4 and chronic lymphoproliferative disorders,5 also drove CML cells into apoptotic cell death (28.6% at 72 and 40.5% at 96 hours of culture). Apoptosis occurred mainly via terminal myeloid differentiation of the leukemic clone, as demonstrated by cytospin morphological and cytotoxic examinations.

Taken together, these findings further support the importance of focusing on inducers of programmed cell death as promising new agents in the management of chronic phase CML, and provide a rationale for the employment of either purine analogs or ATRA in pilot clinical trials.

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Correspondence

Table 1. Laboratory parameters and clinical manifestations at onset in six patients with TTP.

<table>
<thead>
<tr>
<th></th>
<th>Hb g/dL</th>
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<th>LDH U/L</th>
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<th>Kidney findings</th>
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<td>MD</td>
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<td>no</td>
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<td>DA</td>
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<tr>
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<td>13.0</td>
<td>2450</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>PLM</td>
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<td>1743</td>
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</tr>
<tr>
<td>BS</td>
<td>7.2</td>
<td>11</td>
<td>1570</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

All patients received the first plasma exchange employing fresh frozen plasma, and CPP was used in the following procedures. PE was performed daily until normalization of the platelet count and serum LDH levels.

Two patients (B.S. and P.M.L.) died 8 and 5 days, respectively, after beginning plasma exchange, and the addition of high-dose IV immunoglobulins in one case did not produce any effect. Clinical remission was reached in four patients. In one case, neurological disorders at onset such as amnesia and paresis improved after three PE procedures.

Normalization of platelet count was observed after 7, 11, 13 and 17 plasma exchange procedures, respectively. Our experience confirms the data reported by Perotti et al. regarding hematological recovery, while the neurological disorders that appeared during the treatment in two patients did not seem to be influenced by the addition of CPP.

These observations seem to limit the efficacy of CPP as compared to fresh frozen plasma in the treatment of TTP.

Riccardo Centurioni
ALESSANDRO CECAPOLLI
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References

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Lymph node myeloid metaplasia associated with chronic neutrophilic leukemia

Sir,

Chronic neutrophilic leukemia (CNL) is a rare disorder characterized by neutrophilia due to mature elements and organ infiltration, including both hepatosplenomegaly and lymph node infiltration. Around 78 cases have been reported up to now and no one else has described the presence of myeloid metaplasia in lymph nodes as we have in this study.

A 68-year-old man presented weight loss, enlarged lymph nodes, hepatosplenomegaly and ascites. WBC count was 156 x 10^9/L (84% neutrophils, 1% monocytes, 2% basophils, 3% bands, 2% atypical lymphocytes, 5% metamyelocytes, 5% myelocytes). Hemoglobin was 8.7 g/dL, platelets 68 x 10^11/L, uric acid was 15.8 mg/dL, alkaline phosphatase 2457 U/L, LDH 915 U/L, granulocytic alkaline phosphatase 300 U. Renal and liver function were normal. Paracentesis revealed ascitic liquid with 3.6 x 10^9/L cells (85% mature neutrophils). Bone marrow biopsy displayed increased cellularity and granulocytic hyperplasia compatible with CNL. Cyto genetic study was normal (46,XY). Molecular biology did not demonstrate a bcr-abl translocation. A lymph node biopsy showed massive substitution of the normal lymph node architecture by hematopoietic cells, including elements of all three series; within the granulocytic line numerous polynuclear cells were conspicuously intercalated among immature cells. Megakaryocytes were also frequent, and some of them presented phagocytic phenomena.

Myeloid metaplasia has not been previously described in CNL. Chronic neutrophilic leukemia was recently characterized as a distinct myeloproliferative disease with a specific molecular marker (bcr/abl with C3/A2 junction). Our finding of myeloid metaplasia is consistent with the myeloproliferative nature of CNL.

José A. Pérez-Simón
JULIO M. HERNÁNDEZ-RIVERA
Teresa Flores

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Prolonged low doses of oral etoposide may be effective in individual patients with advanced lymphoproliferative disorders refractory to aggressive chemotherapy

Sir,

Etoposide, a semisynthetic podophyllin derivate, is currently employed in the treatment of several malignancies. The antitumor efficacy of etoposide is highly schedule dependent and it has been demonstrated that five-day administration is superior to single day administration. Oral etoposide has greatly facilitated the use of multiple-day schedules and the drug displays good activity in many extrahematological malignancies as well as in lymphomas.

From December 93 to May 94, we treated with prolonged low doses of oral etoposide 24 patients with advanced hematological malignancies not eligible for further intensive approaches due to age >60 years and/or severe previous infective complications. Of these, ten patients had ALL, 8 AML, 4 NHL and 2 had CML.

Etoposide (50 mg/m² per day) was administrated orally for 21 consecutive days; patients who showed a response or stable disease on day 28 received a second and a third cycle of the same treatment. Responder patients received maintenance etoposide at the same dosage 10 days/month until relapse.

Three patients (12.5%) died during the first cycle of intracerebral hemorrhage (1 patient) or infective complications (2 patients); no other toxic deaths were observed. All other patients received at least 2 cycles. Two ALL and 1 NHL patient (12.5%) obtained a complete remission of short duration (2, 3, 7 months); 1 ALL and 2 NHL patients (12.5%) achieved a partial response. No patient with myeloproliferative disease attained a response. Data from responder patients are shown in Table 1.

As for toxicity, 15/24 patients (62.5%) suffered febrile episodes during treatment (4 sepsis, 6 bronchopneumonia, 1 fungal sinusitis and 4 fever of unknown origin). One patient developed an intracerebral hemorrhage, while 8/24 patients (33.3%) displayed cutaneous hemorrhagic manifestations. Ten patients (41.6%) had mild nausea (WHO < 2) and vomiting, and 6/24 (25%) mucositis (WHO 2).
Despite the heterogeneity and low number of patients treated, some preliminary observations can be made. The 25% overall response rate achieved is encouraging and compares favorably with other single-agent approaches, as well as with intra-avenous etoposide.4

Previous studies have also reported encouraging results using oral etoposide in untreated elderly AML patients.5 By contrast, the results reported in ALL patients are disappointing.6 No AML patient in our study responded. However, ALL patients showed a 30% response rate (2/10 CR and 1/10 PR). Overall, oral etoposide achieved better results in advanced lymphoproliferative disease (6/14 responder patients) than in advanced myeloproliferative disease (0/10 responder patients). The reason for this behavior is unclear.

The toxicity of the schedule was acceptable and no patient discontinued the treatment because of nausea. As expected from the advanced disease status and heavy pretreatment of these patients, median response and survival duration were short. The use of oral etoposide in less advanced disease and/or its association with other drugs are possible ways of improving these results.

**References**


Circulating antiplatelet antibody specificity in children with immune thrombocytopenic purpura at onset

**Sir,**

immune thrombocytopenic purpura (ITP) is caused by the interaction of platelet reactive antibodies with platelet surface antigens, which determines accelerated platelet destruction of antibody-coated platelets. Two forms of childhood ITP may occur: a syndrome similar to adult chronic ITP, and an acute self-limiting form of the disease. Only few reports have been published about antiplatelet antibody specificity in paediatric ITP; some of them4,1 studied the specificity of circulating antiplatelet antibodies by testing patient sera by immunoblotting. However, certain conformational antigens on platelet membrane are destroyed by this technique. Moreover, these reports concerned small pediatric ITP populations. It was suggested that the presence of circulating anti-GPllb/Illa antibodies may be useful in differentiating acute from chronic ITP in children;4 however, in a recent pediatric survey6 no difference between the two ITP forms was found. We investigated the specificity of circulating antiplatelet antibodies of ITP children at onset, in order to assess whether it may represent a marker of evolution of the disease. Sera were collected from 74 ITP children (4 months to 13 years, mean age of 5.5 years) at onset before beginning therapy. Forty-nine patients recovered within 6 months from the initial diagnosis (acute ITP), whereas 25 patients developed chronic disease (mean duration 2.2 years, range 1 to 5 years). Antibody specificity was assessed by indirect MAIPA assay refined according to Kiefel et al7,8; we looked for anti-GPllb/Illa and anti-GPllb/IIXG antibodies.

Anti-GPllb/Illa antibodies were found in 19/49 (38.8%) and in 8/25 (32.0%) acute and chronic ITP, respectively. Antibodies to GPllb/IIXG were detected in 15/49 (30.6%) acute ITP and in 7/25 (28.0%) chronic ITP. Thus, in our experience we did not find any significant difference between acute and chronic ITP, evaluating both anti-GPllb/Illa and anti-GPllb/IIXG antibodies. This study reports on the investigation of circulating antiplatelet antibodies specificity in the largest sample of acute and chronic ITP children at onset ever analyzed at our institution. We conclude that circulating antiplatelet IgG specificity in childhood ITP at onset does not represent a marker to the early recognition of those patients devoted to chronicize. We cannot rule out that autoantibodies against platelet antigens other than GPllb/Illa and GPllb/IIXG were responsible for thrombocytopenia in some of our patients; moreover, antiplatelet IgM should be investigated especially in acute ITP patients. Finally, more useful information could be obtained performing directly MAIPA on patient’s platelets.

**References**


Hodgkin’s disease in Brazil: a clinicopathologic study

**Sir,**

the behavior of HD in Brazil, namely its epidemiology, historical distribution, clinical and pathological stages, and the
potent for cure with conventional treatment is not well-known but is of both practical and scientific importance. Spector et al. described good results in treating 59 HD patients from rather low socioeconomic background using C-MOPP/ABV chemotherapy. The authors carried out a study in 134 cases of adult patients (age above 15 years; 76 males and 58 females) from 1985 to 1994. HD appeared predominantly in males (R=1.31); the incidence peaked between 21 and 30 years and presented a descending curve after 30 years of age.

The most frequent histologic type was nodular sclerosis (NS)(50.4%) followed by mixed cellularity (MC) (34.6%), lymphocyte depletion (LD) (9.0%) and lymphocyte predominance LP (5.2%) (Table 1). NS-I type prevailed over NS-II (30.8% and 19.6%, respectively). The cervical region, followed by the spleen and retroperitoneum, was the most frequent primary sites of disease. A bulky mass was found in 20% of the cases, mostly in the mediastinum. Bone marrow (BM) was involved in 16.5% of the patients: none LP type, 3.0% in NS, 6.8% in MC and over 40% in LD type. Anemia was directly related to BM infiltration (p=0.003). B symptoms as well as higher levels of mucoproteins were more frequent in males (p=0.02 and 0.03, respectively). In contrast, early clinical stage occurred mainly in females (p=0.004). Probability of survival after 5 years was 83%. Disease free survival was 52%. No statistically significant differences were found between sexes, NS and MC types or NS-I and NS-II subtypes. Complementary factors that negatively influenced the survival were BM infiltration (p=0.02), lymphopenia (p=0.01) and serum mucoproteins above 7 mg/dL (p=0.01).

Table 1. Distribution of histologic types according to sex.

<table>
<thead>
<tr>
<th>histologic type</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>%*</td>
<td>n.</td>
</tr>
<tr>
<td>LP</td>
<td>76</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>MC</td>
<td>33</td>
<td>43.4</td>
<td>13</td>
</tr>
<tr>
<td>NS-I</td>
<td>17</td>
<td>22.5</td>
<td>23</td>
</tr>
<tr>
<td>NS-II</td>
<td>13</td>
<td>17.1</td>
<td>13</td>
</tr>
<tr>
<td>LD</td>
<td>8</td>
<td>13.1</td>
<td>4</td>
</tr>
<tr>
<td>unclassified</td>
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<td>1.3</td>
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</tr>
<tr>
<td>total</td>
<td>76</td>
<td>100</td>
<td>58</td>
</tr>
</tbody>
</table>

These findings demonstrate that the NS type is possibly the most frequent histologic type, at least in Southeast Brazil, a pattern similar to that found in developed countries.

One interesting clinical feature concerns the period between the first sign of clinical symptoms and medical diagnosis. We observed that this period was significantly shorter in women and in NS-II type, when compared to other types, particularly NS-I. Among men, a history of disease up to 24 months could be detected. On the other hand, the shorter disease history interval among NS-II patients may be due to more rapid lymph node enlargement. This fact points to different biological behavior for NS-I and NS-II, although this difference did not influence response to therapy or prognosis.

One of the most important aspects in our study is related to the distribution of patients in clinical stages. The validity of the Ann Arbor staging system has been established. In our study, a large number of cases were in advanced stages (68.8%) and presented B symptoms (67.2%). This is different from developed countries, where such cases rarely exceed 50%. The larger extent of disease at diagnosis in our patients could also be documented by the number of sites of involvement, the prognostic significance of which has already been stressed. All these features point to a delay in diagnosis of HD in our population. This is also confirmed by the high incidence of BM involvement, anemia, high ESR, and mucoprotein levels, as well as a high frequency of lymphopenia. Nevertheless, response to treatment was adequate according to the results described for the same stages and with the same therapy schedules.

References


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MEETING ANNOUNCEMENTS

24th National Congress of the Italian Association of Pediatric Hematology and Oncology
Bologna, Italy, Palazzo dei Congressi
June 1-3, 1997

Any further information available through the Scientific Secretariat, Studio E.R. Congressi, via Riva Reno 47, 40122 Bologna, Italy. Tel. +39.51.235293. Fax. +39.51.235296.

26th Annual Meeting of the International Society for Experimental Hematology
Cannes, France, Palais des Festivals
August 24-28, 1997

Any further information available through the Scientific Secretariat, Package Organisation, 53, rue Vauvan, F-69006 Lyon, France. Tel. +33.4.78241806. Fax. +33.4.72741833.