Long-term survivors. A high percentage of curability with a consequently large number of inhibitors or alkylating agents; furthermore, APL patients presented chemotherapy, which in some cases included topoisomerase II inhibitors. The responsibility of this phenomenon was attributed to the frequency of the t(14;18) translocation as well as the total number of circulating t(14;18)-positive cells in the individuals studied. At present, possible effects of higher cumulative doses cannot be excluded.

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To the editor:

Second malignancy after treatment of acute promyelocytic leukemia: experience of GIMEMA trials

In a recent issue Lagatiola et al reported 5 cases of therapy-related myelodysplastic syndrome-acute myelogenous leukemia (tMDS-AML) following acute promyelocytic leukemia (APL) in a cohort of 77 patients who achieved a complete remission (CR) after chemotherapy according to GIMEMA 0389 and AIDA trials. The authors, on the basis of these data, concluded that the observation of tMDS-AML is an emerging problem that could increase in the future. The responsibility of this phenomenon was attributed to chemotherapy, which in some cases included topoisomerase II inhibitors or alkylating agents; furthermore, APL patients presented a high percentage of curability with a consequently large number of long-term survivors.

Between 1982 and 1997 in the GIMEMA APL trials (LAP 0383, 0389, and 0493), 1145 patients were recruited (261 patients in the 0389 trial, 113 patients in the 8303 trial, and 771 patients in the 0493 trial). Details on treatment schedule were previously reported. All trials included anthracycline administration (daunorubicin or idarubicin) during the induction and consolidation phases. Maintenance therapy was randomly administered only in the 8303 trial (no therapy vs methotrexate plus 6-mercaptopurine for 2 years) and in the 0493 trial (no therapy vs ATRA vs methotrexate plus 6-mercaptopurine vs 2 + 3 for 2 years). Among these patients, only 4 males (0.3%) aged 36, 38, 61, and 76 years, respectively, developed a second primary malignancy (SPM) (kidney, bowel, melanoma, and thyroid, respectively). All these patients were treated according to the 0493 trial. The median latency between APL diagnosis and SPM was 6.6 months (range, 3.8-7.6 months). The median follow-up was 2.2 years (range, 0-13.8 years). None of them received methotrexate plus 6-mercaptopurine as maintenance therapy. Two patients died from progression of secondary malignancy (bowel and melanoma), without signs of APL relapse, after 3 and 12 months, respectively. The other 2 patients are still alive without signs of relapse of either of the malignancies after 46 months (kidney) and 97 months (thyroid).

Based on these results it may be concluded that low-level radiation exposure up to 400 mSv has no significant effect on the frequency of the t(14;18) translocation as well as the total number of circulating t(14;18)-positive cells in the individuals studied. At present, possible effects of higher cumulative doses cannot be excluded.

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malignancy at 5 years was 0.43 (95% CI 016-1.15) and was unchanged at 10 years.

Our data allow some interesting considerations. The probability of developing an acute leukemia in patients who received chemotherapy or radiotherapy for a previous malignancy (PM), including acute leukemia, is a well-known occurrence: secondary forms constitute approximately 8% to 10% of all acute leukemias and are usually myeloid.6

The main reason for this event is that several drugs employed in the treatment of the PM, particularly topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines), and combined chemotherapy including alkylating agents, are considered potentially mutagenic. As suggested by Latagliata et al,1 the use of intensive chemotherapy to cure APL, with the inclusion of topoisomerase II inhibitors, has a potential role in inducing a tMDS-AML.7 In our cohort of patients, the number of secondary malignancies is lower than expected in the normal population. The estimated cumulative incidence at 5 and 10 years is also lower than that expected. Furthermore, the brief latency between the onset of the 2 malignancies leads to the hypothesis that the second malignancy is probably not related to the carcinogenic action of the drugs employed for the treatment of APL, but perhaps to a chance association only.

These considerations suggest that APL treatment is not relevant in inducing the onset of secondary nonhematological malignancies. In contrast, the action of topoisomerase II inhibitors, which represent one of the main anticancer drugs used in APL, could favor the development of a tMDS-AML with a leukemogenic action on blood stem cells.

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To the editor:

Oxidation of glutathione peroxidase–deficient red cells by organic peroxides

Red cells from mice with a disrupted glutathione peroxidase-1 (GSHPx-1) gene have no GSHPx activity, since GSHPx-1 is the only isoform of GSHPx found in the erythrocyte. In a recent article in Blood,1 we reported that these enzyme-deficient red cells are not oxidized by exogenous hydrogen peroxide any faster than wild-type cells. This strongly supports the view that catalase is the predominant enzyme protecting red cells from attack by exogenous hydrogen peroxide. However, this conclusion also raises a question about the role of GSHPx in the red cell. In this regard, we noted that while catalase is completely specific for H2O2, GSHPx is able to reduce organic peroxides as well, suggesting that the distinctive role of GSHPx might be to detoxify organic peroxides. To test this, wild-type and GSHPx-deficient red cells2 were exposed to a range of compounds known to hemolyze red cells (cumene peroxide, t-butyl peroxide, primaquine, paraxat). Oxidation of hemoglobin (Hb) was used as an endpoint for oxidative damage. Preliminary studies also assayed K efflux, which is increased by organic peroxides.3,4 However, the alteration in K efflux was found to follow temporally the oxidation of Hb, indicating that Hb oxidation was an earlier indicator of oxidative damage. Of these compounds, the GSHPx-deficient red cells showed differential sensitivity only to organic peroxides. Figure 1 shows a distinct and reproducible difference between wild-type and GSHPx-deficient cells in their sensitivity to organic peroxides.

What might be the evolutionary benefits of an erythrocyte mechanism for detoxifying organic peroxides? Are there circumstances when organic peroxides might arise in animal issues? Circumstantial evidence is found in the observation that all microorganisms have enzymatic activities, AhpC/F, that reduce organic peroxides.5-10 Although these enzymes are peroxiredoxins and have no structural relationship to eucaryotic GSHPx, they exhibit similar catalytic capacities and are able to reduce cumene peroxide and t-butyl peroxide. These enzymes protect the bacterium against damage by organic peroxides, strengthening their functional similarity to GSHPx. Interestingly, deletion of genes for these organic peroxide reductases sometimes,9,10 but not always,8 attenuates the virulence of pathogenic strains, suggesting that organic peroxides may be part of the macrophage bactericidal response. Reactions between the H2O2 of the respiratory burst and

Figure 1. Oxidation of hemoglobin in intact erythrocytes by organic peroxides.

● indicate wild-type red cells; ○, GSHPx-deficient red cells.
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