further explored in randomized trials. At present, however, the data on the activity of anthracyclines and ifosfamide is more solid, and determination of the best schedule for combining the two agents should probably have priority.

In the editorial accompanying our paper Dr. Verweij indicated that the use of GM-CSF could have influenced the therapeutic activity seen [8]. This contention is based on the data of Edmondson et al. [9, 10] that suggested that the efficacy of a combination of IFOS, doxorubicin, mitomycin-C and cisplatin could be improved by systematic administration of molgramostim (GM-CSF), the product we used in our trial, at 5 µg/kg every 12 hours. In that pilot study all patients received GM-CSF during 14 days after the combination was given, and nine patients also received this agent prior to chemotherapy, from day −6 to day −3. One partial and four complete remissions were observed in 11 patients with STS, with three of the responders progressing within the year, and all responsive types corresponding to histologic subtypes sensitive to IFOS and doxorubicin. This data from a small number of patients is not especially remarkable and can be attributed to hazard rather than to a GM-CSF effect. In our study there was a similar response rate either before or after patients received GM-CSF, although administration criteria and dosing were completely different from those utilized by the Mayo Clinic investigators. Objective remissions were observed in 11 of 23 patients who never received or before receiving GM-CSF, and in six of 22 patients who responded while receiving GM-CSF (χ², P = 0.155, two-tailed). In our opinion, there is no consistent data to support or preclude the use of a specific type of CSF in patients with STS nor to justify a randomized study.

There are many biological aspects of STS still unknown that may explain the discordant results reported by different investigators. Objective remissions were observed in 11 patients who never received or before receiving GM-CSF, and in six of 22 patients who responded while receiving GM-CSF (χ², P = 0.155, two-tailed). In our opinion, there is no consistent data to support or preclude the use of a specific type of CSF in patients with STS nor to justify a randomized study.

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References


Oral ipriflavone (7-isopropoxy-isoflavone) treatment for elderly patients with resistant acute leukemias

It has been reported that the flavonoid, quercetin (3,3',4',5,7-pentahydroxy-flavone), inhibits cell growth in several cancer cell lines and is capable of increasing the antiproliferative activity of cytotoxic agents [1–2]; quercetin is able to inhibit leukemic cell proliferation and colony formation by acute myeloid and lymphoid leukemic progenitors without suppressing normal myelopoiesis [3, 4]. Moreover, we have shown that quercetin has a pronounced synergistic antiproliferative effect with cytarabine (ara-C) on both HL-60 cell line proliferation and the clonogenic capacity of primary human leukemic cells [5].

Eleven patients with acute leukemias, nine of them with acute myeloid leukemia (AML) and two with acute lymphoid leukemia (ALL; median age 70, range 53–76), were treated with ipriflavone. Seven of the 11 were resistant to conventional chemotherapy; 3 were in first relapse and 1 was in second relapse.

Ipriflavone was started as second-line treatment after the failure of conventional cytotoxic treatment in patients in poor clinical condition. In fact, five patients presented cardiovascular disease that had worsened following anticancer treatments, and four presented diabetes requiring insulin treatment.

A three-time daily dose of oral ipriflavone 600 or 400 mg was administered alone in four patients, in combination with hydroxyurea (1 g/day) in four cases, with onconvin (2 mg/week) in two cases and ara-C (15 mg/twice daily for 15 days monthly) in one patient.

After two months of treatment, three patients (two AML and one ALL) had achieved partial remissions lasting 11, 7, and 10 weeks. One patient was treated with ipriflavone alone, one concomitantly with hydroxyurea and one with onconvin.

Seven of 11 thrombocytopenic patients (median platelet count before starting ipriflavone treatment 20 × 10⁹/l, range 10–35) showed increases in platelet count with a consequent reduction in supportive treatment (median platelet count 35 × 10⁹/l, range 30–55). Eight patients presented marked reductions of mucocutaneous hemorrhages. We observed no severe side effects of ipriflavone aside from moderate nausea and vomiting in three patients and mild liver toxicity in one. The compliance of ipriflavone (6–12 capsules/day) was good.

Preliminary data presented in this study show that treatment with ipriflavone, alone or in association with other anti-neoplastic agents, is well tolerated with good compliance and without hematological or extra-hematological side effects. In
three patients ipriflavone induced partial remission, and although the median survival of our patients after the onset of ipriflavone treatment was only 30 weeks, the supportive care requirements were markedly reduced together with hemorrhagic manifestations. This therapeutic effect may be due to both the increase in platelet counts and the protection of vascular wall demonstrated for other flavonoids used in the therapy of venostatic diseases [6].

Flavonoids inhibit in vitro human leukemic cell growth and, in particular, ipriflavone reduces the in vitro clonogenic capacity of patients' leukemic progenitors [4] with a slight reduction of clonogenic capacity by normal bone marrow progenitors.

The mechanism of the antiproliferative activity of flavonoids remains to be fully clarified. Since flavonoids interact with a variety of enzymes it is possible that their antiproliferative activity is mediated by these interactions [7, 8].

In view of the positive results obtained with ipriflavone and the fact that quercetin appears to be more effective in inhibiting in vitro growth-factor-B1 in this cells. Blood 1995; 86: 3654-61.

Telomerase or telomersyn?

An article on telomerase at a meeting of our journal club was recently the main focus of discussion. Why telomerase? Does this enzyme bring death or life to the substance telomere?

We know that telomerase is the enzyme that synthesizes telomeric DNA, leading to telomere extension [1]. What does this suffix 'ase' actually mean? According to one dictionary, it is used in naming enzymes and sometimes added to a part of the whole of the name of the compound which the enzyme decomposes [2], while according to another the suffix 'ase' indicates an enzyme - moreover, a destructive substance [3].

When we look at the classification of enzymes [4] we see, in general, that when this suffix comes at the end of a substrate's name, it indicates that the word has a catabolic character, e.g., lipase, urease, amylase, protease, nucleotidase, nucleosidase, ATP-ase, DNase, RNase; whereas when it comes at the end of a word which defines reactions such as oxidation, dehydrogenation, hydroxylation, transfer, transamination, polymerization, or phosphorylation, the word - the enzyme - declares its active involvement in such reaction.

After all, the suffix 'ase' at the end of the name of a substrate such as telomere seems to imply a catabolic effect on the ribonucleoprotein, the only known mechanism that can stabilize telomere length in vertebrate organisms [5, 6]. In conclusion, for a better understanding of terminology, why not 'telomersyn' as an abbreviation of telomere synthetase?

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References