Appendix

List of participating Centers

Divisione di Ematologia, Ospedale SS. Antonio e Biagio, Alessandria; Clinica di Ematologia, Nuovo Ospedale Torrette, Ancona ; Divisione di Ematologia, Ospedali Riuniti, Bergamo; Istituto di Ematologia e Oncologia Medica "Seràgnoli", Policlinico S.Orsola, Bologna; Clinica Pediatrica II, Università di Bologna, Policlinico S.Orsola, Bologna; Divisione di Ematologia, Trapianto di Midollo Osseo, Ospedali Civili, Brescia; Istituto di Clinica Medica, Cattedra di Genetica Medica, Università di Cagliari,Cagliari; Cattedra di Ematologia, Azienda Ospedaliera di Careggi, Firenze; Dipartimento di Ematologia, Ospedale S.Martino, Genova; Divisione di Medicina IV, Istituto G.Gaslini, Genova; Isituto Clinico Humanitas, Oncologia ed Ematologia, Sezione Trapianti di Midollo Osseo Milano; Divisione di Ematologia , Dpt. di Scienze Mediche Oncologiche e Radiologiche, Università di Modena, Modena; Clinica Pediatrica, Ospedale Nuovo S.Gerardo, Monza; Cattedra di Med. Interna ed Ematologia, Ospedale "S.Gerardo de Tintori", Monza; Divisione di Ematologia, Università Federico II, Napoli; Dept. di Ematologia Pediatrica, Azienda Ospedaliera "Santobono Pausillipon", Napoli; Centro Leucemie Infantili, Clinica Onco-Ematologica Pediatrica, Università di Padova, Padova; Cattedra di Ematologia, Centro Trapianti di Midollo Osseo, Università di Parma, Parma; Dipartimento di Ematologia, IRCCS Policlinico San Matteo e Università, Pavia; Dept. Medicina Clinica e Sperimentale, Sezione di Ematologia ed Immunologia Clinica, Università di Perugia, Ospedale Monteluce, Perugia; Divisione di Ematologia, Centro Trapianti di Midollo,Ospedale Civile, Pesaro; Divisione di Ematologia, Ospedale S.Chiara, Università di Pisa, Pisa; Divisione di Ematologia, C.U.R. TMO e Terapie Emato-Oncologiche Sovramassimali "A. Neri", Ospedale Bianchi-Melacrino-Morelli, Reggio Calabria; Servizio di Ematologia, Arcispedale S. Maria Nuova, Reggio Emilia; Cattedra di Ematologia, Università La Sapienza, Roma; Divisione di Ematologia, Ospedale S. Eugenio, Università Tor Vergata, Roma; Divisione di Ematologia, Istituto di Sem. Medica, Policlinico Gemelli, Roma; Azienda Ospedaliera "S. Camillo Forlanini", Unità Operativa di Ematologia e Centro Trapianti di Midollo Osseo, Ospedale S.Camillo, Roma; Divisione di Ematologia, Ospedale Magg. S.G. Battista, Università di Torino, Torino; Clinica Pediatrica III, Ospedale Regina Margherita, Università di Torino, Torino; Istituto per l'Infanzia, Clinica Pediatrica Istituto Burlo Garofalo, Trieste; Cattedra di Ematologia, TMO, Ospedale S.Maria Misericordia, Udine; Divisione di Ematologia, Presidio Ospedaliero S.Bortolo, Vicenza.

Clinical usefulness of arsenic trioxide in the treatment of acute promyelocytic leukemia

Following initial reports from China,[1,2] several groups have established arsenic trioxide (As_2O_3) is a highly effective therapy for acute promyelocytic leukemia (APL).[3] Importantly, this newly revisited old compound proved active in APL patients resistant to retinoids (RA) such that it is nowadays widely employed for therapy of early relapses and/or for patients who undergo disease recurrence while on RA treatment. Toxicity of As_2O_3 appears limited and includes cardiac disturbances (Q-T prolongation), hyperleukocytosis and the RA syndrome. These side effects are well controlled in most instances, although cases of sudden deaths (probably of cardiac origin) and severe hepatotoxicity have been reported.[1-3] Finally, long-term toxicity in the context of APL is less defined. While there is no question on the efficacy of this agent, its place in current treatment of APL is still a matter of investigation.

In this issue of Haematologica, Leoni *et al.*[4] contribute to this issue suggesting that As_2O_3 treatment is a convenient approach for relapsed APL patients who are to be submitted to stem cell transplantation (SCT). Indeed, they report a favorable outcome in 5/7 patients receiving this therapeutic strategy for RA-resistant or relapsed APL. This and other experiences on recurrent APL suggest that, although not curative, As_2O_3 can re-induce these patients into hematologic remission with mild toxicity thereby preparing them better for highly aggressive approaches such as SCT. Indeed, in the series of Leoni *et al.*,[4] SCT was successful and accompanied by limited toxicity in most cases. Some issues may be pointed out for future investigations on the role and place of this drug in APL.

While it appears a useful re-inducer of remission, As_2O_3 does not seem able to eradicate the disease. Hence, chemotherapy and SCT have been added in most studies to consolidate remission.[3] It is not clear, however, how many cycles of As_2O_3 should be administered prior to SCT. Assuming that molecular remission (i.e. polymerase chain reaction negativity for PML/RARα) is the therapeutic objective, it may be argued that 2 cycles instead of one may be used prior to SCT as they would more likely result in molecular remission. Similarly, the role (if any) of pre-SCT chemotherapy after As_2O_3-induced re-induction should be investigated. One major problem related to these issues concerns the low numbers of

patients we are dealing with. In fact, given the favorable outcome of APL with front-line RA plus chemotherapy, only few patients may be the subject of investigation for treatment of relapse.[5-7] Finally, the effectiveness of As_2O_3 for consolidation of RA+chemotherapy induced remission as well as its potential synergism with retinoids front-line are being assessed in ongoing studies.

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Cell division cycle manipulation and cancer treatment: a solid promise or just a dream?

The exact number, function and phenotype of cells present in a specific tissue are under a strict control which results in a wonderful balance between a resting status, proliferation, differentiation (both terminal or reversible), and apoptosis.

Cancer might be thought of a disease characterized by a deregulation of this balance with a partial loss of differentiation features and apoptotic response along with a relative increase of proliferative capability. Thus, it is not surprising that the molecular components of the cell division cycle machinery are frequently altered in human neoplasias. The cell-cycle of all post-embryonic eukaryotic cells (including malignant cells) is divided into four phases, namely: G1 phase (the period prior to DNA synthesis), S phase (period of DNA synthesis), G2 phase (period between DNA synthesis and mitosis) and M phase (mitosis). Collectively, G1, S and G2 are called the interphase, the cell cycle period distinct from division of the nucleus (mitosis) and cytoplasm (cytokinesis).[1-3]

The duration of the S, G2 and M phases are remarkably similar in many different cells, while the greatest variation is seen in the duration of G1. At some point late in G1, called the restriction or R point, a cell becomes committed to go through the remainder of the cell cycle. Thus, variations in cell cycle time are mostly due to variations in the length of G1 up to the R point.[1-3]

A large body of evidence indicates that transformed cells show alterations which involve the mechanisms regulating the transversing of the R point and result in a premature S phase entry. Such a phenomenon might cause ineffective DNA repair, the accumulation of genetic damage and, finally, the progression towards a malignant genotype. As well known, most of these aberrations cause the loss of activity of *RB*, *p53* and *CDKN2A* (*p16^{INKa}*) genes.[4-6]

Additional type of alterations, particularly overexpression, have been evidenced in several other genes encoding proteins which regulate some step of cell division cycle. Their frequency is, however, lower than that of the three genes mentioned above. In conclusion, it has been generally thought that all human cancers show at least one genetic aberration which allows the loss of cell cycle control.

A logical consequence of these premises is that approaches which might restore physiologic control of the cell cycle could be useful in the treatment of cancer. These are the bases of the study by Rui *et al.* reported in the issue of February 2002 of Haematologica.[7]

However, as often occurs in all aspects of experimental and clinical medicine (and, unfortunately, human life) there is no, or little, direct interplay between hopes and reality. In all instances, before analyzing some strategic possibilities of manipulating cell division cycle in order to treat human cancers, it is necessary to consider some points.

First, cell division cycling is a process which involves *all* cells of the body, and its manipulation might be very harmful for normal cells in that it could cause catastrophic side effects.