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## Editorial, comments and views

# Are we sure we all do the same things? Results from a GITMO survey on basic practices in allogeneic bone marrow transplantation

Variability and uncertainty affect all human measurements. In particular, in medical sciences, statistical approaches are needed to explain which part of variation belongs to chance and which part is explained by the association, to various extent, with known factors, the so-called prognostic factors.

The experimental method relies on standardization and repeatibility. Thus, in clinical trials, methods are stated in protocols and experimental procedures have to be performed in accordance. Some practices, however, have a long standing history and are commonly considered *standard practices* by those involved in the field. In clinical allogeneic bone marrow transplantation (BMT), for example, superficially similar methods of prophylaxis against graft-versus-host disease (GVHD), varicella zoster herpes virus (HZV) and *Pneumocystis carinii* pneumonia (PCP), are adopted by mosts centers. What is commonly taken as *standard*, however, is not always such.

We have recently conducted a brief survey among the GITMO (*Gruppo Italiano Trapianto di Midollo Osseo*) Centers in order to investigate the degree of standardization of basic transplant-related-procedures, such as GVHD and anti-infectious prophylaxis. These findings were briefly presented at the annual meeting held in Rome on May 7-8, 2001.

Thirty-three Centers (60%), representing 68% of allogeneic transplant activity in Italy, answered a specific questionnaire which was mailed by the GITMO secretariat to all Centers.

The first issue of the survey was about GVHD prophylaxis. The association between cyclosporin A (CsA) and methotrexate (MTX) still represents the most common regimen, used by the 94% of the centers, whereas CsA + micofenolate mofetil (MMF) represents the first option in the remaining 6%. The original study, which showed the superiority of the association CsA and short course MTX in respect to CsA alone,[1] was performed using 15 mg/m$^2$ on day +1, and 10 mg/m$^2$ on days +3,+6 and +11, whilst the actually applied schedules (Table 1) vary from 5-5-5 mg/m$^2$ on days +1, +3, +6, to 10-8-8 mg/m$^2$ on days +1, +3, +6. Of note, only 13/33 (39%) of the Centers adhere to the classical Seattle schedule, 6/33 (18%) Centers use four MTX administrations, but with doses lower than in the original study and the remaining 11 administer only 3 doses of MTX (ranging from 5-5-5 mg/m$^2$ to 10-8-8). The use of folinic acid rescue after MTX also varied depending on *local* criteria regarding its appropriateness (yes, 55% of the Centers; no, 36%; not known, 9%) and scheduling (doses and timing, which vary from 5-30 mg every 6 h for 24 h to 50 mg in a single dose after 24h).

Nevertheless, a number of analyses, one quite recently,[2] have suggested that a fourth dose of MTX significantly affects the probability of severe acute GVHD, relapse and survival.

With respect to CsA administration, doses and infusion times reach quite a high level of variability, ranging from 1 mg/kg/bw in 1-2 h to 3-5 mg/kg/bw in a continuous perfusion (Table 2).

Whatever the doses and infusion times, the administration of CsA is always modulated according to the plasma levels of the drug which, perhaps surprisingly, result quite similar both for the *fast* (less than 12 hours) and for the *slow* (more than 12 hours) infusions (Figure 1).

The meaning of such levels is clearly different, since they represent the trough level in the case of *fast* infusions or the steady-state level for the continuous or *slow* infusions. The impact of similar criteria in adjusting the CsA doses is, in fact, unknown.

HZV prophylaxis also exhibits a high degree of variability with respect to doses, schedules and criteria (Table 3).

Similar results are found for the prophylaxis against PCP (Table 4).

**Table 1. Methotrexate doses and schedules among the BMT Centers. The use of folinic acid rescue also varies in doses (6-50 mg) and scheduling (every 6 hours for 24 hours to once after 24 hours).**

| | | *BMT Centres (%)* |
|---|---|---|
| Methotrexate schedules | Three administrations | 43 |
| | Four administrations | 57 |
| Dosages (mg/m$^2$, on days +1/+3/+6/(+11) from BMT) | | |
| | 15/10/10/10 | 39 |
| | 12/10/10/10 | 6 |
| | 10/8/8/8 | 18 |
| | 15/10/10 | 27 |
| | 10/8/8 | 12 |
| | 5/5/5 | 3 |
| Folinic acid rescue | | |
| | Yes | 55 |
| | No | 36 |
| | not known | 9 |

**Table 2. Cyclosporin A administration for GVHD prophylaxis. High variability in the doses and infusion times has been found.**

| *Cyclosporin A administration* | |
|---|---|
| Once daily administration | BMT Centers (%) |
| 1 mg/kg in 1-2 h | 12 |
| 3 mg/kg in 4-8 h | 12 |
| 3 mg/kg in 12 h | 3 |
| 5 mg/kg in 12 h | 3 |
| 1 mg/kg in 18-24 h | 12 |
| 1-3 mg/kg in 22 h | 3 |
| 2 mg/kg in 24 h | 9 |
| 2-3 mg/kg in 20 h | 3 |
| 3 mg/kg in 18-24 h | 21 |
| Twice daily administrations | |
| 1 mg/kg in 3 h | 3 |
| 3 mg/kg in 2 h | 6 |
| 3 mg/kg in 6 h | 3 |
| 1-3 mg/kg in 4 h | 3 |
| Not applicable | 7 |

**Table 3. Varicella zoster virus prophylaxis.**

| | *BMT Centers (%)* |
|---|---|
| Drugs | |
| Acyclovir | 91 |
| Valacyclovir | 6 |
| Foscavir | 3 |
| Doses (Acyclovir) | |
| 10 mg/kg | 21 |
| 20 mg/kg | 9 |
| 30 mg/kg | 42 |
| 75 mg/kg | 6 |
| 500-1000 mg/m$^2$* | 3 |
| other | |
| Duration of prophylaxis after BMT | |
| <1 month | 18 |
| 1-3 months | 18 |
| 4-6 months | 33 |
| 7-9 months | 6 |
| 10-12 months | 22 |
| Other | 3 |
| Criteria for modulating the prophylaxis | |
| cGVHD | 28 |
| VUD transplants | 28 |
| CMV Status | 14 |
| N of CD4$^+$ | 8 |
| More than one | 22 |

*In the second column the percentage of Centres is reported. The most commonly used drug is Acyclovir. The main schedules related to Acyclovir are reported.*
**Pediatric centres*

**Table 4. Prophylaxis against Pneumocystis pneumonia after allogeneic BMT. The most commonly used drug is cotrimoxazole. Doses and duration of the prophylaxis are reported as well as the main reasons for changing its duration.**

| | *BMT centers (%)* |
|---|---|
| Drugs | |
| Cotrimoxazole | 91 |
| Pentamidine | 6 |
| Azithromycin | 3 |
| Doses (Cotrimoxazole) | |
| 1 g x 2/twice a week | 43 |
| 1 g x 2/trice a week | 18 |
| 0.5 g/d | 6 |
| 5-10 mg/kg/twice a week | 18 |
| 20 mg/kg/2,3 times/week | 3 |
| Not known/other | 6 |
| Duration | |
| <3 months | 22 |
| 4-6 months | 36 |
| 7-9 months | 6 |
| 10-12 months | 18 |
| Other | 9 |
| Not known | 9 |
| Reasons for modulating the duration of prophylaxis | |
| CGVHD occurrence | 84 |
| CD4$^+$ blood levels | 8 |
| VUD transplants | 8 |

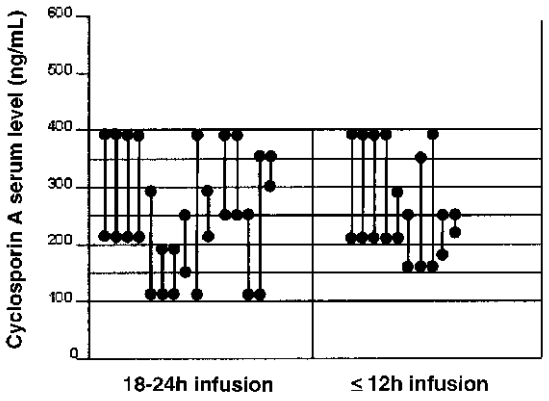


**Figure 1. Cyclosporin A therapeutic ranges in patients receiving a single daily administration. Thick lines relate to slow infusions, thin lines to fast infusions. Each line indicates one Center. It appears that CsA doses are adjusted according to the same serum level irrespective of the infusion time.**

The results of this survey are likely to reflect the practices of GVHD and anti-infectious prophylaxis in Italy, since information was received by more than half the Centers, performing about 70% of the transplants made per year.

This survey shows that a great variability exists in the application of basic standard procedures of allogeneic transplantation. Many of these procedures are clearly well accepted in the clinical setting, despite the lack of supportive published data or evidence-based medicine. They represent the current opinion of the transplant Centers about the issues in question. Procedures are known to vary, but the variability found here is much broader and deeper than one would expect, even from previous European surveys aimed at defining the general policies, not the practical details, in transplantation.[3,4]

Such a variability regards factors which influence the outcome of BMT. Hence, it could act as a background noise, a confounding effect, which could amplify variance, in particular that part of variance we cannot explain. These findings have great implications for the practice of transplantation. First they show that basic procedures are performed very differently among the Centers, despite being nominally the same: this could deeply affect the interpretation of results, in particular after the pooling of multicenter data.

Second, on a theoretical level, these findings lead to two mutually exclusive hypotheses: either these *standard* procedures are not so important for the outcome, and, in this case, the least toxic and cheapest schedule should be chosen or, on the contrary, they are important, and in this case, they should be clearly stated, when a trial has been performed and published.

Since we believe in the second hypothesis, we propose, for any multicenter study – and GITMO studies in particular – that when investigators are planning a trial, they should standardize the basic procedures precisely instead of defining only the variables under study, such as response variables. The value of studies constructed in this way will be much empowered in comparison to those conducted with the wildly different practices we all employ nowadays.

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## Appendix

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## 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/RAR$\alpha$) 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