A pathogen reduction clinical trial in retrospect

Paolo Rebulla

Blood Transfusion Service, Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Introduction

Blood transfusion is regulated in Italy by the Ministry of Health (MoH) through the national competent authority, named the National Blood Centre (*Centro Nazionale Sangue*, CNS).

In the early 2000s, the development of commercial systems to inactivate pathogens in blood components prompted the Italian MoH to plan technology assessments of the available technologies, under the co-ordination of the CNS. As a first step, a working group was formed with the task of developing a project, named the Italian Platelet Technology Assessment Study (IPTAS), aimed at a parallel evaluation of the clinical effectiveness of platelets treated with the Intercept® (Cerus, Concord, CA, USA) and Mirasol® (Terumo BCT, Lakewood, CO, USA) pathogen reduction systems.

In 2007, the working group started drafting the project, which was awarded a research grant by the MoH in 2009 (grant ISS 2007646931, *Ricerca Finalizzata* 2009). Representatives from both Cerus and Terumo BCT were invited to contribute comments and proposals on the project. Both companies agreed to meet a proportion of its cost.

The working group selected a "non-inferiority" design for a national multicentre randomised clinical trial aimed at the evaluation of the clinical effectiveness of pathogen reduced platelets *vs* standard platelets. The primary end point of the study was percent of onco-haematology patients with grade 2 or greater bleeding. The latter was defined using the modified World Health Organization (WHO) bleeding scale developed by the investigators of the Platelet Dose (PLADO) study[1]. Based on local historical records supporting an expectation that 20% of control patients would develop one or more grade 2 or greater bleeding, a non-inferiority margin of 11% (representing the upper 97.5% confidence limit of the increase in the percent of bleeding actually detected) was considered appropriate in relation to expected benefits of pathogen reduction. To ensure appropriate statistical power, the study (clinicaltrials.gov identifier: 01642563) required a sample size of 207 patients for each arm and technology, i.e., 828 patients in total. Patient enrolment started in October 2010 and the study was terminated on 30 June 2014, after the enrolment of 424 evaluable patients, due to financial limitations.

A partial analysis of the results obtained in the 424 patients was presented in abstract form at the 2015 AABB annual meeting[2]. The full intention-to-treat and per-protocol analyses will be published elsewhere. A brief outline of the study methodology is given in Table I.

In this commentary, I will briefly discuss some lessons learnt through the development and management of the IPTAS project, which are reported with the expectation that they may be valuable to other investigators involved in similar trials and to competent authorities in charge of regulating pathogen reduced blood components. This commentary includes the personal opinions of the Author, which do not necessarily reflect those of the other IPTAS investigators.

Problems, difficulties, failures

Funding

The Italian MoH supported IPTAS with a research grant of 530,000 Euro[3]. This sum (which was in the high range of national grants for similar trials) was used to support data collection performed during the period October 2010-June 2014 by six clinicians in charge of patient selection, enrolment and daily monitoring at the six clinical centres participating in the study. In addition, both manufacturers of the pathogen reduction systems tested in the study provided the pathogen inactivation

Table I - Main features of the Italian Platelet Technology Assessment Study (IPTAS).

Two non-inferiority randomised clinical trials carried out in parallel with a common protocol in onco-haematology platelet recipients.
Pathogen reduced platelets in additive solution *vs* standard platelets in additive solution.
Three clinical centres using the Intercept® technology; three clinical centres using the Mirasol® technology.
Primary end point: percent of patients with WHO grade 2 or greater bleeding.
Secondary end points: post-transfusion platelet count increments, blood component use; transfusion reactions and adverse events; mortality.
IPTAS biorepository including patient's plasma and buffy coat collected at each transfusion and segments of standard and pathogen reduced blood components transfused during the study.

WHO: World Health Organization.

Blood Transfus 2017; **15**: *329-32* DOI 10.2450/2017.0340-16

kits and the irradiation devices free of charge to the blood transfusion services participating in the study.

During the 4-year duration of our study, there have been several opportunities to discuss operational hurdles to the development of our project with a number of colleagues belonging to the transfusion medicine community of other countries and regulatory jurisdictions. In this regard, I shared with many colleagues the classical difficulties related to clinical protocol design and approval, patient enrolment and daily monitoring, data accuracy and study oversight, statistical analysis and final reporting. Moreover, I also learnt that the financial support per patient enrolled in our study would have been considered significantly below a minimum threshold for a randomised clinical trial of this size and complexity in many jurisdictions. More specifically, two highly respected specialists estimated that the cost of performing IPTAS in their countries might have amounted to 10 times the budget described above.

This comment led me to explore the literature to find some cost references in view of possible future studies. Indeed, I found support for the estimates from our international colleagues in the $ 26,000 average cost per patient enrolled in haematology studies reported in March 2015 by Pharmaceutical Research and Manufacturers of America (PhRMA)[4]. Another study on the cost of conducting clinical research published in 2003[5] found that "[on] average, 4,012 hours (range 1,512 to 13,319 hours) were required for a government-sponsored trial, and 3,998 hours (range 1,735 to 15,699) were required for a pharmaceutical industry-sponsored trial involving 20 subjects with 17 office visits, or approximately 200 hours per subject. Thirty-two percent of the hours were devoted to non-clinical activities, such as institutional review board submission and completion of clinical reporting forms. On average, excluding overhead expenses, it cost slightly more than $ 6,094 (range $ 20,98 to $ 19,285) per enrolled subject for an industry-sponsored trial, including $1,999 devoted to non-clinical costs".

The above figures should not be considered as a discouragement to perform clinical research outside "ideally rich" settings. Nonetheless, they may be helpful in the early phases of study planning to prepare a reasonable budget based on published cost analyses.

Based on the above, I learnt lesson number one: don't start a project with a budget below a reasonable threshold.

Patient accrual

The IPTAS missed the primary end point due to insufficient sample size. Our initial expectation was to complete the planned enrolment of 828 patients in four years. This expectation was supported by platelet transfusion reports retrieved from the six participating institutions at the time of study protocol development. Table II shows the number of platelet units and the number of recipients transfused in 2006 at the centres participating in the IPTAS project. The apparently reassuring number of a cohort of more than 1,200 patients receiving more than 10,000 adult platelet doses per year led us to believe that patient accrual would not be difficult. After an encouraging enrolment of 180 patients during the period October 2010-December 2011, patient accrual progressively decreased during 2012-2014. Among a number of factors which may have contributed to this decline, we identified two main possible causes. First, several large, "richly supported" clinical trials sponsored by big pharmaceutical companies prescribed that patients enrolled in such trials could not be enrolled into other clinical trials. Thus, competition with other more generously financed studies may have contributed to reducing the initial enthusiasm and commitment at the IPTAS centres. Second, the IPTAS protocol prescribed that patients could be enrolled only once, thus preventing patients admitted for successive courses of chemotherapy to be enrolled again. I consider both the above provisions on inclusion/exclusion criteria methodologically correct and appropriate.

Our difficulties in matching the required accrual taught me lesson number two: be very careful and specific in the analysis of the patient cohort from which the study population will be accrued. Next time, I would also investigate number and type of "competing" trials annually performed at the participating institutions, and annual patient return rate. Moreover, retrospective literature analysis of "accrual capabilities" in different

Table II - Number of platelet units and number of recipients transfused in 2006 at the centres participating in the Italian Platelet Technology Assessment Study (IPTAS) project.

Centre	A	B	C	D	E	F	Total
N. of platelet apheresis units	591	100	669	22	1,330	1,219	3,931
N. of buffy-coat platelet units	501	700	0	2,200	1,032	882	5,315
N. of platelet rich-plasma platelet units	0	60	1,800	146	988	0	2,994
N. of platelet transfusion recipients	170	145	300	100	250	286	1,251

N.: number.

geographical areas and professional networks could facilitate the development of large, international trials able to enrol the required sample size within a reasonable time interval. Examples[1,6,7] of accrual capabilities are reported in Table III.

Primary end point

Primary end points of clinical trials must be clinically relevant. When we designed the IPTAS protocol, we selected bleeding (more specifically, the percent of patients developing one or more grade 2 or greater bleeding events using a modified WHO bleeding scale) as primary outcome. Percent of days with bleeding events and post-transfusion platelet count increments (a surrogate marker of platelet transfusion effectiveness) were included in the secondary outcomes. We selected "percent of patients with one or more bleeding episodes" rather than "percent of days" for the primary outcome as its complement to 100% represents the fraction of patients free of bleeding episodes, an outcome of very high clinical relevance. A clear defect of the primary outcome that we selected relates to its inability to distinguish between patients with one bleeding episode only from those experiencing multiple episodes. This defect can be partially corrected (as we did) by reporting a detailed analysis of number (%) of patients with 0, 1, 2, 3 or more bleeding episodes and the bleeding organ/site. However, WHO grade 2 bleeding is generally considered of limited clinical significance. The selection of grades 3 and 4 bleeding only, which are of clearly higher clinical significance, would be impractical as they occur with much lower frequency than grade 2 and their use as a primary outcome would require a very large sample size.

The identification of an ideal and practical primary outcome for these studies is still a matter of debate and I did not really learn any lesson in this regard from the IPTAS project. In future studies, I would suggest focusing on the number of days with bleeding, as a "day with bleeding" represents an event of discomfort for the patient which requires medical attention and generates cost. Clearly, expert statistical advice would be necessary to control bias generated by multiple, recurrent events detected in individual patients[8-10].

The "good stuff"

Just a brief overview is needed here since the main purpose of this article was to share lessons learnt with the wisdom of hindsight (a sort of self-questioning) from the IPTAS project, while the results of the study will be published elsewhere.

But briefly, although we failed the primary outcome, IPTAS collected clinically relevant outcomes on the safety and effectiveness of pathogen reduced platelets prepared with two commercial technologies in relatively large groups of onco-haematology recipients. Moreover, it provided robust evidence on the differential consumption of blood components in treated *vs* control patients which will be valuable for local cost analyses on pathogen reduction technologies currently performed by the Italian MoH.

Additional valuable features of the IPTAS project were the parallel testing of the Intercept® and Mirasol® technologies in two independent clinical trials using a unique protocol and the randomisation of centres to using one or the other inactivation technology, thus reducing bias due to local preferences.

Due to legitimate commercial sensitivity related to the outcomes of our study, it was wise to include in the IPTAS protocol a highly detailed pre-specified format for data presentation to be used for publication purposes.

The large IPTAS biorepository including patient and product samples is currently being investigated to study HLA alloimmunisation. We believe that this precious biological material will be the source of important studies in the next few years.

Finally, a very important outcome of the IPTAS project was the consolidation of a national network of transfusion medicine specialists able to perform clinical research under the co-ordination of the National Blood Centre.

Conclusions

The IPTAS project has left me with some unanswered questions. First, what is the best, or most appropriate, study design for clinical trials on pathogen reduction in blood components? With respect to the classical format of "experimental" clinical trials (that we followed in the IPTAS project) my understanding of the more recent

Table III - Patient accrual in selected platelet transfusion studies.

Study	Duration (months)	Total enrolment	N. of centres	N. of patients/year/centre
PLADO[1]	48	1,351	26	13
Study on bleeding prophylaxis *vs* no prophylaxis[6]	66	398	8	9
TOPPS[7]	60	600	14	8.6
IPTAS	45	424	6	18.8

N.: number; PLADO: Platelet Dose study; TOPPS: Trial of Prophylactic versus No Prophylactic Platelet Transfusions; IPTAS: Italian Platelet Technology Assessment Study.

literature on the methodology of "pragmatic" clinical trials suggests that the latter may offer important advantages for studies whose main purpose is to determine if a particular procedure will be or will not be implemented in a particular setting[11]. Further discussion on the advantages and disadvantages of pragmatic *vs* experimental clinical trials may be helpful for the design of future studies.

Second, who is the best monitor of clinically relevant outcomes in these studies? A fully dedicated, specifically trained nurse recruited from outside (i.e., independent from) the clinical ward where the study is performed, or a member of the staff routinely in charge of patient treatment? Having spent my whole professional career in close contact with clinicians in charge of onco-haematology transfusion recipients I tend to trust more the latter than the former for their ability to detect 'really meaningful' clinical outcomes. I am fully aware that this perceived (and possibly biased) advantage must be balanced with more difficult standardisation of the "clinical eye" monitoring the patients and with a lower propensity of busy clinicians to spend significant portions of their valuable time to accurately fill in the case report forms necessary to document the outcomes of clinical studies.

Whatever the study design, we cannot ignore that there is no escaping the need for not only clinically relevant but also statistically significant evidence. Luckily, disastrous haemorrhage is an infrequent event in today's onco-haematology patient. The need for sufficiently large sample sizes should encourage the blood transfusion and regulatory communities to facilitate the performance of international, rather than only national clinical trials, with the obvious benefit of shorter time for the collection of the scientific evidence necessary to answer the questions that remain.

Funding and resources

Grant *Ricerca Finalizzata* 2007 by Ministry of Health.

Acknowledgements

The Author acknowledges the collaboration of the National Blood Centre and of the staff of the clinical centres and the Blood Transfusion Services participating in the IPTAS project.

The Author declares no conflicts of interest.

References

1) Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 2010; **362**: 600-13.
2) Rebulla P, Vaglio S, Aprili G, et al. Clinical efficacy and safety of platelets in additive solution treated with two commercial pathogen reduction technologies. Transfusion 2015; **55**: 3A-4A.
3) Ministero della Salute. Istituto Superiore di Sanità (ISS) - Progetti 2007. Available at: http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=1117&area=Ricerca%20sanitaria&menu=finalizzata. Accessed on 29/11/2016.
4) Pharmaceutical Research and Manufacturers of America (PhRMA); Battelle Technology Partnership Practice. Biopharmaceutical industry-sponsored clinical trials: impact on state economies. Available at: http://www.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf. Accessed on 29/11/2016.
5) Emanuel EJ, Schnipper LE, Kamin DY, et al. The costs of conducting clinical research. J Clin Oncol 2003; **21**: 4145-50.
6) Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet 2012; **380**: 1309-16.
7) Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med 2013; **368**: 1771-80.
8) Cook RJ, Heddle NM, Rebulla P, et al; Biomedical Excellence for Safer Transfusion (BEST) Working Party of the International Society for Blood Transfusion. Methods for the analysis of bleeding outcomes in randomized trials of PLT transfusion triggers. Transfusion 2004; **44**: 1135-42.
9) Cook RJ, Heddle NM. Clinical trials evaluating pathogen-reduced platelet products: methodologic issues and recommendations. Transfusion 2013; **53**: 1843-55.
10) Stanworth SJ, Hudson CL, Estcourt LJ, et al; TOPPS study investigators. Risk of bleeding and use of platelet transfusions in patients with hematologic malignancies: recurrent event analysis. Haematologica 2015; **100**: 740-7.
11) Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008; **337**: a2390.

Correspondence: Paolo Rebulla
Blood Transfusion Service
Foundation Ca' Granda Ospedale Maggiore Policlinico
Via Francesco Sforza 35
20122 Milano, Italy
e-mail: paolo.rebulla@policlinico.mi.it