Blood Reviews 29 (2015) 351–357

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

From evidence to clinical practice in blood and marrow transplantation

Nandita Khera *

College of Medicine, Mayo Clinic, 5777 E Mayo Blvd, Phoenix, AZ 85054, USA

ARTICLE INFO

Keywords:
Clinical trials
Blood and marrow transplantation
Practice patterns
Evidence uptake
Dissemination and implementation research

ABSTRACT

Clinical practice in the field of blood and marrow transplantation (BMT) has evolved over time, as a result of thousands of basic and clinical research studies. While it appears that scientific discovery and adaptive clinical research may be well integrated in case of BMT, there is lack of sufficient literature to definitively understand the process of translation of evidence to practice and if it may be selective . In this review, examples from BMT and other areas of medicine are used to highlight the state of and potential barriers to evidence uptake. Strategies to help improve knowledge transfer are discussed and the role of existing framework provided by the Center for International Blood and Marrow Transplant Registry (CIBMTR) to monitor uptake and BMT Clinical Trials Network (BMT CTN) to enhance translation of evidence into practice is highlighted.

1. Introduction

Clinical science advances by discovering new treatments and proving that they are better than what is currently available. Adoptions of results from clinical trials is unpredictable, and there are conflicting reports about whether the publication of results of randomized clinical trials (RCTs), even in high impact scientific journals, is enough to change practice patterns. Translation of research evidence into clinical practice requires a series of steps to help move knowledge gained from basic laboratory and clinical investigation to its application in clinical and community settings — the so-called 'discovery–delivery continuum' (Fig. 1). One of the prerequisites for optimum dissemination and implementation of an intervention is that it be useful, appealing, and relevant to those who would apply it. There is no doubt that "if we want to advance evidence-based practice, we need more practice-based evidence" [1]. Practice based evidence to meet the needs of all stakeholders in the process does not come solely from artificially controlled research, but is developed by synthesis of various evidence sources.

The field of blood and marrow transplantation (BMT) has evolved from bench to bedside, moving from the original studies in rodents and other primates in the early 1950s, first human transplants in 1957 to the current state of the science with haploidentical and cord blood transplants and genetically engineered immunotherapy. Although well-conducted, rigorous, multi-center RCTs in BMT may indicate scientific progress, they are resource intensive, expensive, difficult and time-consuming to conduct. The effort to conduct the trials may be wasted if they do not ultimately change clinical practice and advance the science which is not limited to academic centers alone. A survey in 2012 showed that at least 20% of the BMT programs were not associated with a teaching hospital and only 44% of the programs were affiliated with a National Cancer Institute Comprehensive Cancer Center [2].

This review aims to describe the current state of evidence uptake in the field of BMT. Since few studies assessing the process of dissemination and implementation of research findings to clinical practice have been conducted in BMT, a review of findings from other fields including oncology, critical care medicine and cardiology is presented. Challenges in the area of knowledge transfer that may be relevant to the practice of BMT are described. This review addresses three major questions relevant to evidence uptake in BMT: 'How representative are trial patients of the entire patient population, and are the trial results generalizable to similar patients treated off protocol?' 'What is the impact of clinical trials on clinical practice patterns?' 'Are investigative sites/researchers who help generate the evidence more likely to implement results of trials than non-investigative sites?' For each of these questions, we review the theoretical principles behind the question, summarize relevant literature in other fields of medicine, and conclude with a discussion of relevance in the context of BMT. The review concludes by summarizing the steps which can help bridge the gap between evidence and practice in BMT.

1.1. How representative are trial patients of the entire patient population, and are the trial results generalizable to similar patients treated off protocol?

Research is important for advancing the practice of medicine, and RCTs are regarded as the gold standard in clinical research. In general, RCTs use rigorous experimental design with randomization to compare two or more treatment approaches in a selected group of patients. However, the process of applying the evidence generated from the RCTs to clinical care may highlight some limitations of clinical trials [3].

* Tel.: +1 480 342 3047.
E-mail address: khera.nandita@mayo.edu.

http://dx.doi.org/10.1016/j.blre.2015.04.001
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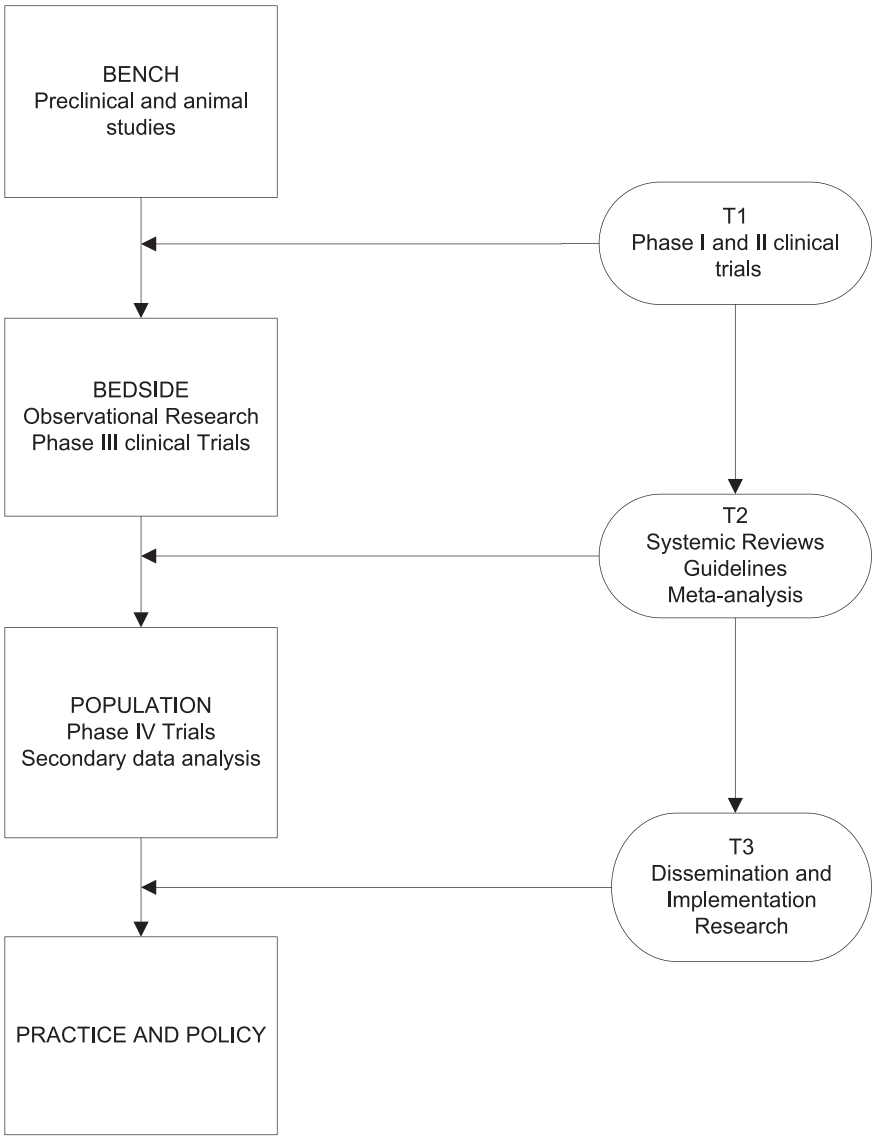

Fig. 1. Phases of translational research.

It is not clear how representative trial participants are of 'real world' patients and whether results of the trials are applicable to individual patients seen in practice. If the general population of patients differs from trial participants, or the results of the treatment differ when given outside the trial, then the conclusions of clinical trials are not generalizable. The deviation from generalizability often starts with restrictive inclusion and exclusion criteria for the trial which gives rise to selection bias. Usually patients that are enrolled on trials are younger, with fewer comorbidities and a better performance status though they may or may not have a higher risk disease [4,5]. Patients from rural areas, from racial/ethnic minorities such as African-Americans and Hispanics, and those with lower socioeconomic status are usually under-represented in trial populations due to a variety of reasons [6]. It is possible, that better outcomes in patients enrolled in clinical trials compared to non-trial participants that have been reported by several studies are because of the recruitment of a relatively good prognostic group [7–9]. Absence of strategies to control for the potential confounding factors in the studies that compared trial and non-trial participants led Peppercorn et al to report that there is insufficient evidence to conclude there is a trial effect on outcomes [10]. Some other studies and another large review also suggest that the outcomes of patients who participate in trials are comparable to similar patients treated in a similar fashion off-trial [10–13].

In the last decade, many large trials performed by the BMT Clinical Trials Network (BMT CTN) represent landmark advances in the field of BMT. One of such studies: BMT CTN 0201 evaluated the efficacy of peripheral blood (PB) vs. bone marrow (BM) for unrelated donor (URD) transplants [14]. We recently conducted a study comparing the outcomes of patients who were treated on this multicenter randomized study with other patients who appeared eligible and were treated in a similar fashion but off-study, using data from Center for International Blood and Marrow Transplant Registry (CIBMTR) [15]. In a pattern somewhat different from general oncology trials and studies in other areas of medicine, the trial participants and non-participants were found to be comparable in age, race/ethnicity, disease distribution and comorbidities. Differences were seen in disease risk, performance status and conditioning regimen intensity. Survival was found to be comparable between study participants and non-participants, suggesting no trial