The right to care and the expectations of society —controversial stem cell therapy in Italy

Maurizio Bifulco & Patrizia Gazzerro

A debate has started [1–2] about a controversial stem cell therapy in Italy that exposes the difficult interaction between scientists, health care, doctors' duties and patients' rights. The case involves an experimental therapy based on adult mesenchymal stem cells that can differentiate into bone and connective tissue, and that were administered to a paediatric patient suffering from metachromatic leukodystrophy. The cells were produced by the privately owned, non-profit Stamina Foundation and administered at the public hospital of Brescia, Italy. However, they were not produced in accordance with Italy's safety standards and have not been rigorously tested for efficacy and safety. Despite the lack of experimental evidence and the negative opinion of the Italian Drug Agency and Italian College of Health, Italy's Ministry of Health authorized compassionate use of the therapy in response to public pressure. Scientists around the world have reacted by criticizing the government for authorizing an untested stem cell therapy, which could create a dangerous precedent.

Although the quality and safety of therapies should be a prerequisite to their use, drugs that were not fully tested in humans have been approved before. Based on the evidence from two *in vitro* studies, 3'-azido-3'-dexoxythymidine (AZT) was the first nucleoside reverse transcriptase inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of HIV-1/AIDS. Although high doses of AZT effectively suppressed HIV in the short term, patients suffered from severe side-effects and eventually developed resistance to the drug [3]. We now know that only triphosphorylated AZT can inhibit the synthesis of proviral HIV DNA [4], and the first AZT given to patients was not triphosphorylated. Moreover, NRTIs could increase the risk of cardiovascular diseases [5]. Today, AZT is part of combination therapy in a smaller dose.

Many drugs that have shown promise in early experimental phases have never entered clinical use, or their use was later suspended. This is the case of tarenflurbil for Alzheimer disease. Unlike symptomatic drugs, tarenflurbil has been shown to modulate γ -secretase activity *in vitro* and *in vivo*, and reduce production of A β 42—the toxic form of β -amyloid. Although a phase 2 trial of the drug was promising, a large phase 3 trial failed to confirm its efficacy in patients with mild Alzheimer disease [6].

Bevacizumab, an angiogenesis inhibitor, has significantly improved the treatment of some types of colon, lung, kidney and brain cancer in combination with chemotherapy. However, in November 2011, the FDA revoked the approval of bevacizumab in combination with paclitaxel for HER2-negative metastatic breast cancers that have not been previously treated, based on clinical trial results that failed to demonstrate a significant reduction of tumour growth and improved quality of life compared with standard chemotherapy. Moreover, several studies suggested that antiangiogenic agents could promote rather than inhibit the formation of metastases [7].

These examples have a common factor: the absence of a cure. They demonstrate the difficult interaction between the right of a patient to treatment, the efficacy and safety of a treatment, the role of regulatory agencies and the hopes of patients. In our opinion, only regulatory agencies or institutions can uphold standards of scientific rigour to ensure the safety and efficacy of therapeutic protocols, and the dignity and quality of life of patients. The definition 'incurable disease' cannot justify the administration of unsafe or ineffective therapies.

However, the timing of preclinical and clinical trials and the procedures for the approval of new drugs need to be simple, fast and appropriate to the needs and hopes

of patients, especially for those suffering from paediatric, rare or rapidly evolving diseases. We believe that these procedures could be improved by international collaboration involving researchers, planning of clinical trials, selection and recruitment of patients, and assessment and publication of results. This is especially true for rare diseases—the few patients and the resulting difficulty of recruiting them to studies hinder the characterization of the disease and the identification of drug targets. It also discourages pharmaceutical companies from investing in these drugs.

Another main problem of the procedures, at least in Italy, is the lack of communication between scientists and regulatory agencies, patients and society. The debilitating nature of disease, pain, loneliness and lack of information lead patients to use unproven therapies or to refuse conventional treatments.

Clinical research should pursue the ultimate goal of patient care, rather than the mere achievement of results that are not always applicable to practice. It must address patients' hopes and expectations, give clear and honest answers, and ensure their dignity and quality of care.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

REFERENCES

1. Abbott A (2013) *Nature* **495**: 418–419
2. Nature (2013) *Nature* **496**: 269–270
3. Larder BA *et al* (1989) *Science* **243**: 1731–1734
4. Yarchoan R *et al* (1986) *Lancet* **1**: 575–580
5. D:A:D Study Group (2008) *Lancet* **371**: 1417–1426
6. Green RC *et al* (2009) *JAMA* **302**: 2557–2564
7. Rapisarda A, Melillo G (2012) *Nat Rev Clin Oncol* **9**: 378–390

Maurizio Bifulco is at the Department of Medicine and Surgery, and Patrizia Gazzerro is at the Department of Pharmacy at the University of Salerno, Italy.
E-mail: maubiful@unisa.it

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