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Communication

Improving Tolerance and Compliance of New Targeted Therapies with Homeopathy: A Major Challenge in Oncology

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Abstract

The application of targeted therapies (TT) in oncology has prolonged survivals and even enabled complete remission of cancers previously considered incurable. With small therapeutic indices, the reduction in dosage or spacing out of the doses of TT due to side effects, represents a significant loss of treatment opportunity for the patients. In the absence of drug interaction and significant side effects, homeopathy used in supportive care improves the quality of life of patients, compliance with oncological treatments and consequently their survival. Based on the author's clinical experience and published studies, a therapeutic regimen for systematic supportive care of TT is proposed in this study. The originality of the treatment lies in combining a symptomatic diluted and dynamised homeopathic medicine with the patient's constitutional homeopathic medicine as well as the isotherapeutic agent used for targeted therapy in 7c (10^{-14}). If needs be, the eponymous organotherapy of the organ most affected by the side effects can be added in 4c (10^{-8}). This therapeutic regimen is well accepted and well tolerated. It has been prescribed to approximately 5,000 patients over 25 years including those patients who were given hormone therapy. Facilitating tolerance and acceptance of targeted therapies is very important in oncology in order to fully benefit from

the TT efficacy. Homeopathy, organotherapy and isotherapy, by supporting the whole body and treating the major side effects, might improve observance and consequently therapeutic results. Clinical trials could be carried out following the designs and protocols presented in this article.

Keywords
Clinical experience; homeopathy; integrative oncology; isotherapy; supportive care; targeted therapies

1. Introduction

Advances in therapeutics in the field of oncology have improved life expectancy and the quality of life of the patients. However, these new treatment strategies may give rise to difficulties and should be ascertained in order to manage these effects with appropriate supportive treatment. Not elucidating the potential side effects might lead to medicine intolerance, reduction of dosage, a gap in the administration of therapy or even a discontinuation of these targeted therapies resulting in a loss of treatment opportunity for the patients.

In the absence of medicine interaction and significant side effects [1], individualised homeopathy in supportive care is very helpful [2]. It can improve the quality of life [3] and consequently the survival of the patients [4, 5]. Well accepted by French oncologists and general practitioners [6], inexpensive [7], it is the complementary medicine most used in supportive care [8]. Homeopathic supportive care is provided in several cancer centres in France and other parts of Europe [9, 10] and patient satisfaction rate is very high [8]. Combined with organotherapy and isotherapy, it can form essential supportive care to patients undergoing treatment with the new targeted therapies [11].

In this article, the author's research and therapeutic experience with cancer patients are discussed. The targeted therapies presented here are recent. No clinical study is available to validate the findings of this article.

2. Background

The new targeted therapies play an important role in the management of cancer. Currently, treatment is administered for a specific type of cell mutation or receptor rather than a type of cancer. These mutations or receptors represent a specific target for these new therapies.

There are two different main therapeutic classes in targeted therapies. The first therapeutic class includes monoclonal antibodies directed against specific receptors present on the surface of cancer cells. They can be recognised by their -mab suffix for Monoclonal Antibody. They are administered intravenously or subcutaneously every two to four weeks. Generally speaking, it is as if they prevented the key from entering the lock, so to speak. As long as the door remains closed, the cancer cell cannot divide and undergo apoptosis.

The second therapeutic class includes small molecules that act on protein tyrosine kinases located in the cell; they are recognisable by their suffix -inib for Inhibitor. They are administered orally daily and, in a way, prevent the key from turning in the lock.

Targeted therapies have a small therapeutic index and are sometimes difficult to tolerate. Thus, they might require tailored supportive care to improve compliance. If excessive side effects occur, the dosage might be reduced or a temporary cessation of treatment is sometimes necessary with the risk of reduced efficacy and loss of opportunity for the patient. Improving compliance can affect the health of the patients more effectively than improving the quality of oncology treatments [12].

3. Homeopathy, Organotherapy and Isotherapy

Homeopathy (from the Greek prefix *homeios*: the similar) is a medical therapy, using infinitesimal dilutions of substances capable of provoking in healthy and sensitive subjects symptoms similar to those presented by the patient [13]. According to the **principle of similarity**, symptomatic medicines such as *Nux vomica* 7c will be chosen for nausea or *Crotalus horridus* 7c for thrombocytopenia [14]. According to the **principle of individualisation**, the medicine also called "constitutional medicine" corresponding to all the symptoms presented by the patient, both physical and psychological, will be chosen [15]. The constitutional medicines most often used in oncology are *Phosphorus* and *Arsenicum album* [5]. According to the **principle of infinitesimality**, homeopathic medicines are prescribed in ultra-high dilution, which explains the absence of major side effects and medicine interactions.

Organotherapy is a diluted and dynamised preparation of organ or hormone extracts of animal origin. It is used with the aim of restoring the proper functioning of the patient's eponymous organ. It is prescribed in low dilution (D6 to D8 that is to say 10^{-6} to 10^{-8}), in addition to the classic homeopathic treatment to support its action on the deficient organ. In homeopathic supportive care I frequently use *Medulla ossium* D6 or D8 to enhance the hematopoietic function or *Nervus medianus* D7 to protect the peripheral nervous system from the neurotoxicity of platinum salts, taxanes, vincristine or bortezomib [14].

Isotherapy (from the Greek prefix *Isos*: the same, the identical) consists in treating a symptom by the agent directly responsible for it. This therapy has been the subject of many experiments, both on animals [16, 17] and plants [18]. I have been using it successfully for 25 years in oncological supportive care, most often in the 7c (10^{-14}) dilution. I have published a small series of clinical cases concerning the beneficial use of Sorafenib 7c in patients with cutaneous side effects of Nexavar® [19].

When prescribed by skilled homeopathic doctors, homeopathy, organotherapy and isotherapy, acting on the pathophysiological mechanism of side effects, has proved, in my experience, to be very helpful in supportive care [11].

4. Improving the Quality of Life of Patients Treated for Cancer: A Real Challenge

The quality of life and life expectancy of cancer patients are positively correlated [20]. The recent randomised, double blind, placebo-controlled trial by Frass *et al* [5] revealed that the homeopathic management of patients with inoperable lung cancer (Figure 1), by improving their quality of life ($p < 0.001$), also leads to a prolongation of the life expectancy of 6 months compared to the placebo group ($p < 0.020$), and of 7 months compared to the control group ($p < 0.001$) (Figure 2).

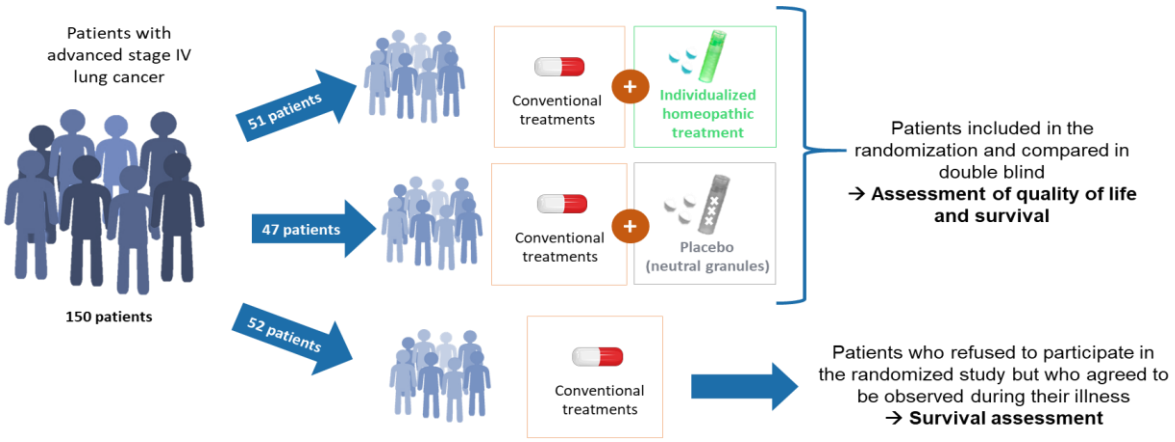

Figure 1 Design of the Frass *et al* study 2020 (Reproduced by kind permission of IHSSCO).

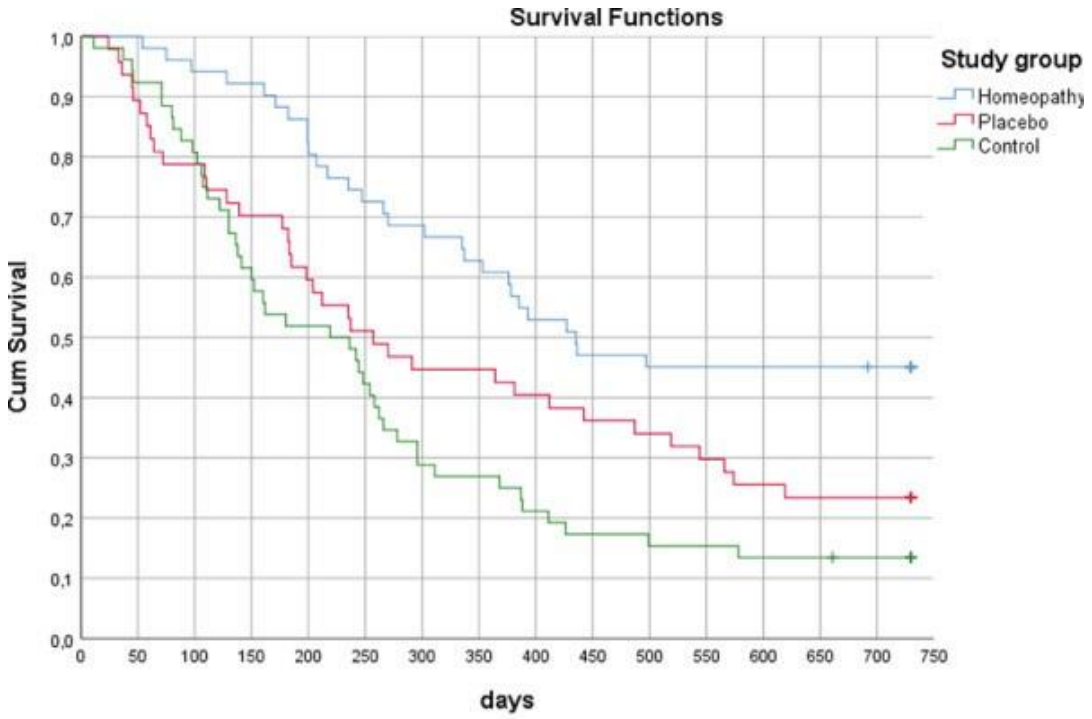

Figure 2 Kaplan-Meier curve on survival after 2 years (Frass *et al* 2020) (Reproduced by kind permission of M.Frass).

5. My Own Approach

In practical terms how do we put together the correct treatment? We only need to follow the principles of **similarity** and **individualisation** to find the homeopathic medicine(s) needed by the patient. A good knowledge of the physiopathological mechanism of the side effects also makes it possible to deal with the **etiological factors**. Taking them into account often proves to be decisive for obtaining good results. I try to anticipate the side effects, to be one step ahead of their occurrence. This requires being very familiar with the potential toxicity of these new therapies and with the prescribing of one or two symptomatic medications to be used as soon as symptoms begin to appear. Organotherapy supporting organs exposed to essential toxicities will be combined with

isotherapy of targeted therapy if possible. Finally, the patient's long term treatment (constitutional medicine) will be prescribed to support their general condition (Figure 3).

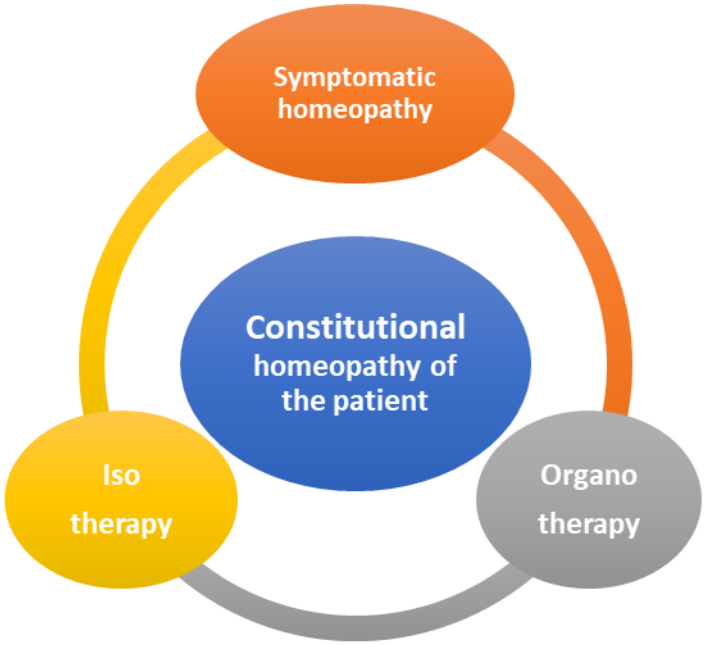

Figure 3 Diagram of the development of the homeopathic supportive care treatment.

6. Immunotherapy

This new therapy, by targeting the immune checkpoints (CTLA-4, PD1, PDL1, etc.), will make it possible to relaunch the immune response of T lymphocytes, which had been dormant until then. Immunotherapy like Ipilimumab (Yervoy®), pembrolizumab (Keytruda®) and nivolumab (Opdivo®) has revolutionised the management of metastatic melanomas, lung, kidney, bladder, thyroid, breast and prostate cancers. Unfortunately, there have been treatment failures, either because the body does not react sufficiently to immunotherapy (insufficient immune defenses), or on the contrary, because the body overreacts, sometimes causing serious autoimmune side effects, requiring corticosteroid therapy and/or permanent discontinuation of treatment [21]. In my therapeutic experience, homeopathic support, carried out from the start of immunotherapy, by balancing immunity, makes it possible to obtain more therapeutic efficacy and to reduce autoimmune reactions [22]. In that respect, I prescribe *Silica* 9c and *Dysprosium metallicum* 9c alternately every other day during the week and the constitutional medicine every Sunday (*Phosphorus, Arsenicum album, Thuja occidentalis* depending on the patient). Thymuline 9c, can stimulate cytotoxic T lymphocytes if the T3 lymphocyte/T4 lymphocyte ratio is below the norm [23] (Figure 4).

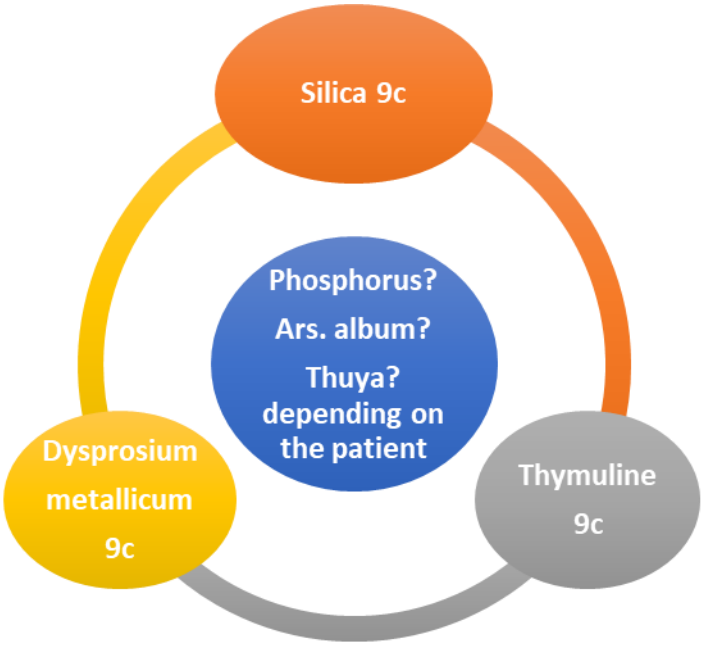

Figure 4 Diagram of the development of the homeopathic supportive treatment for immunotherapy.

7. PARP Inhibitors

These new targeted therapies, olaparib (Lynparza®), niraparib (Zejula®) and rucaparib (Rubraca®) act by blocking the DNA repair mechanisms of cancer cells during mitosis. This reduces the risk of a recurrence of ovarian cancer and of certain breast or prostate cancers. They are particularly indicated in the event of a mutation of the BRCA gene, which is the other possible way of repairing tumour DNA. Homeopathic support, from the start of these targeted therapies, by preventing anaemia and fatigue will lead to better tolerance and better compliance of these treatments [24]. To *China rubra* 7c taken daily to treat the risk of anaemia, I combine *Medulla ossium* D6 or D8 organotherapy, 10 drops one to three times a day, depending on the haemoglobin level, to stimulate erythropoiesis. Anti-PARP isotherapy will be systematically prescribed in 7c, taken daily, but not at the same time as the main conventional medicine. It is important for the isotherapy **not** to be taken at the same time as the conventional medicine. For example if the PARP inhibitor is taken in the morning, then the isotherapy should be taken in the evening (Figure 5).

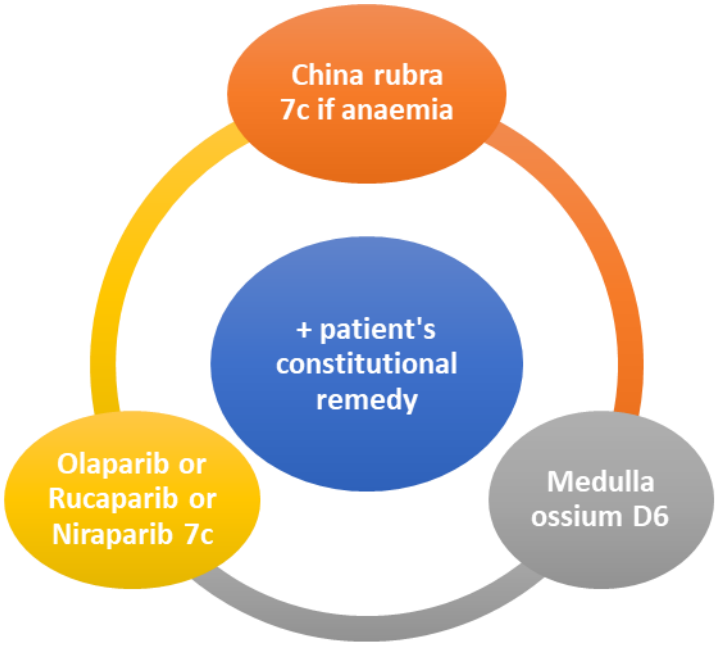

Figure 5 Diagram of the development of the homeopathic support treatment for anti-PARP.

8. CDK 4/6 Inhibitors

These new targeted therapies, palbociclib (Ibrance®), ribociclib (Kisqali®) or abemaciclib (Verzenios®) which are indicated in hormone-dependent, metastatic or locally advanced breast cancers, make it possible to fight against hormone resistance and block the mitosis of cancer cells in G phase, thus preventing their multiplication. Well tolerated and very effective, these targeted therapies give an excellent quality of life for patients who are nevertheless in a metastatic situation. However, grade III neutropenia affects more than half the patients taking palbociclib or ribociclib. Diarrhoea occurs daily in most patients taking abemaciclib.

In our experience, homeopathic support, implemented from the start of the targeted therapy, by preventing neutropenia and diarrhoea, limits the reductions in dosage, the spacing out of treatments and improves compliance [25]. Taking *Natrum muriaticum* 7c, 3 pellets every morning and *Silica* 7c 3 pellets every evening can help to prevent neutropenia. *Medulla ossium* D6 or D8 organotherapy will be prescribed during the week when Ibrance® or Kisqali® is stopped, 2 to 3 times a day to stimulate leukopoiesis. The isotherapeutic palbociclib 7c or ribociclib 7c will also be prescribed daily, to be taken at a different time of the day from the main conventional medicine. For Verzenios ®, *Podophyllum* 5c, 3 pellets, 3 times a day, in the event of diarrhoea and *Natrum sulfuricum* 9c as a preventive treatment for diarrhoea, once or twice a week, supplemented by abemaciclib 7c taken daily (Figure 6).

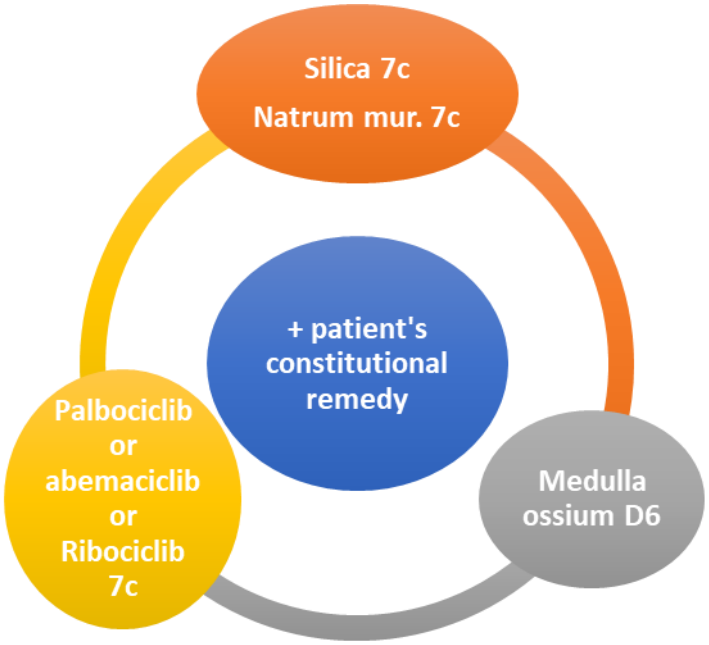

Figure 6 Diagram of the development of the homeopathic support treatment for anti CDK 4/6.

9. Targeted Chemotherapy

In this new therapeutic class, chemotherapy is directly attached to a monoclonal antibody capable of targeting a cancer cell receptor. Thanks to the antibody, the chemotherapeutic agent can attach itself to the target cell, penetrate into the cancerous cell and destroy it. This is the case for trastuzumab emtansine (Kadcyla®), which combines a TDM1 molecule with trastuzumab, an anti-HER2 antibody. It is indicated in HER 2 breast cancers with a score of 3+ in a metastatic or locally advanced situation. This treatment is fairly well tolerated. Fatigue and nosebleeds may be helped by *Phosphorus* 15c, 3 pellets every evening.

Sacituzumab govitecan (Todelvy®) is also a targeted chemotherapy, this time indicated in metastatic, triple negative breast cancers. This medicine targets the Trop-2 protein attached to the surface of breast cancer cells and deposits a govitecan molecule, an active metabolite of irinotecan. The main side effects are neutropenia, diarrhoea, nausea and an allergic risk (Figure 7). Considering that its average annual treatment cost is €500,000, it is extremely essential to ensure that it is well-tolerated.

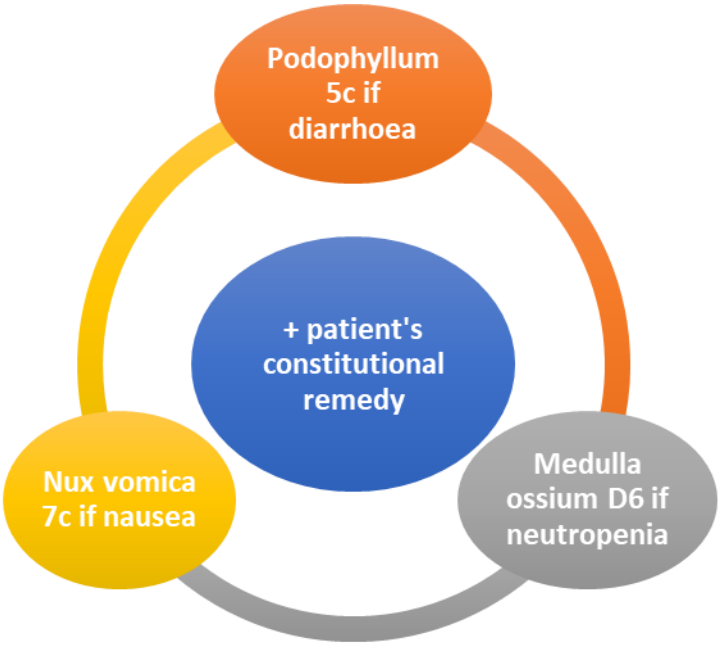

Figure 7 Diagram of the development of the homeopathic support treatment for Trodelvy®.

10. Immunomodulators

Immunomodulators are cytotoxic, immunostimulant, anti-angiogenic and anti-inflammatory. They represent great therapeutic progress for myelomas and for certain lymphomas with a very favourable efficacy/toxicity balance. Currently, the most widely used is lenalidomide (Revlimid®) but pomalidomide (Imnovid®) and thalidomide (Thalidomid®) are also prescribed. Their long-term use after an autograft can significantly delay a myeloma relapse [26].

Commonly associated side effects are transit disorders (constipation or diarrhoea), drowsiness and neuropathy. Haematological monitoring is necessary because of the risk of neutropenia and thrombocytopenia. Fatigue is common and multidisciplinary management might be helpful. Immunomodulators all present risks of well-known foetal malformations, requiring strict contraceptive measures.

Muscle cramps, rash-like skin disorders, phlebitis, water retention and erectile disorders may also occur depending on the reactions of each body to these drugs.

Depending of the main treatment, I use the isotherapeutic Lenalidomide 7c, Pomalidomide 7c or Thalidomide 7c, 3 pellets first thing in the morning. I will also add *Medulla ossium* D6 organotherapy in cases of lower blood lines and *Nux vomica* 7c in cases of digestive disorders. In my clinical experience it has proven to be very effective (Figure 8).

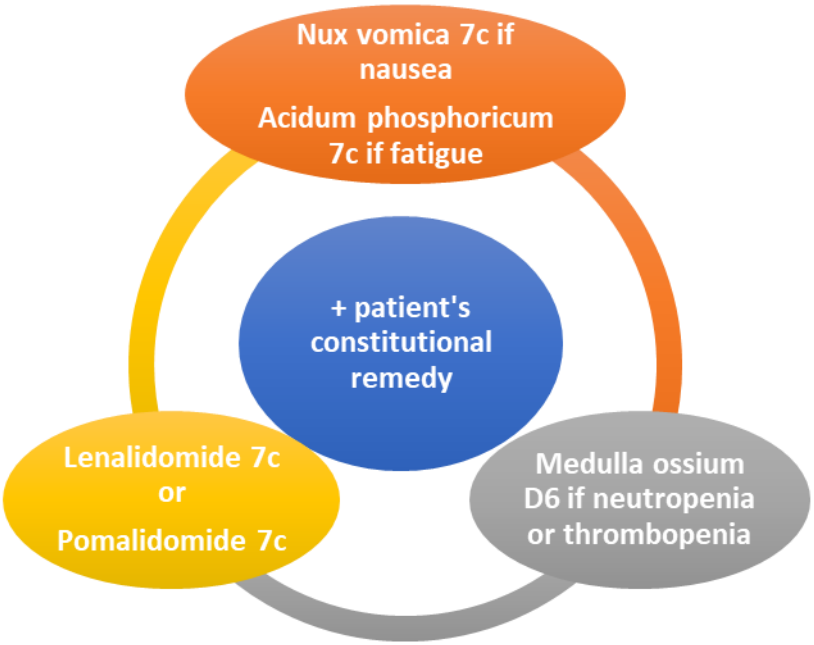

Figure 8 Diagram of the development of the homeopathic support treatment for immuno modulators.

Other possible therapeutic agents, include *Natrum muriaticum* 7c in the morning and *Silica* 7c in the evening in the event of a drop in neutrophils; *Crotalus horridus* 7c once or twice a day, in cases of low platelets, *Cuprum metallicum* 7c in cases of muscle cramps and *Phosphoricum acidum* 7c in cases of fatigue.

To decide on the correct constitutional medicine, one could first look for signs which might indicate the prescription of *Phosphorus, Arsenicum album, Lachesis mutus* or *Phosphoricum acidum*.

11. Targeted Hormone Therapy

Seventy-five to 80% of breast tumours are hormone-responsive, making oestrogens and their receptors prime targets for hormone therapy. These treatments reduce the risk of recurrence by almost half [27]. However, whether for tamoxifen or for aromatase inhibitors (anastrozole, letrozole or exemestane), it is estimated that 35 to 50% of patients stop their treatment prematurely because of joint pain and hot flushes. Stopping this treatment prematurely represents the main reason of treatment failure [28].

A preliminary open study carried out in 2016 by Karp JC *et al*, compared 20 patients starting treatment with anti-aromatases associated with conventional supportive care to 20 patients starting the same treatment also taking *Ruta graveolens* 5c and *Rhus toxicodendron* 9c, five pellets each morning and evening for three months [29]. A statistically significant decrease in joint pain appeared in the group treated with homeopathy ($p = 0.0001$). These positive preliminary results have made it possible to carry out a pragmatic study on a larger number of patients. Their inclusion has been completed and the results are pending. This symptomatic prescription has become a recommendation of the international homeopathic society of supportive care in oncology (IHSSCO) [14]. If necessary, I combine it with isotherapy of the aromatase inhibitor prescribed in 7c taken

daily but at a different time of the day from the main conventional medicine. The most frequent constitutional medicine is *Sepia officinalis* (Figure 9).

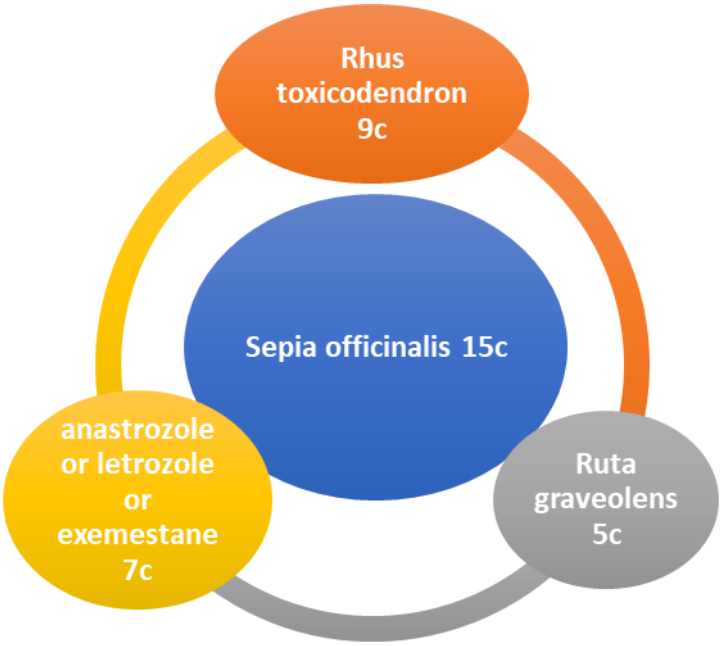

Figure 9 Diagram of the development of homeopathic supportive treatment for aromatase inhibitors.

12. Homeopathy and Enzymatic Interaction with Hepatic Cytochromes

The main metabolism of most of these new therapeutic agents is through cytochrome CYP 3A4. Some natural substances interact with CYP 3A4. For example, St. John's Wort and Asian Ginseng (Panax ginseng) activate CYP 3A4, reducing the activity and the effectiveness of targeted therapies. Conversely, CYP 3A4 inhibitors such as grapefruit, lime and bitter orange juice, Goldenseal and to a lesser extent, liquorice, Aloe vera, black pepper, Schisandra, turmeric, valerian and milk thistle, slow down the elimination of targeted therapeutic agents, increasing their toxicity.

This enzyme induction is dose-dependent. Considering the case of St. John's Wort, which is the most powerful enzyme inducer, a meta-analysis showed that below 4 mg of hyperforin per day, there was no significant effect on CYP3A [30]. Around 120 drops of *Hypericum* mother tincture are required to obtain 3 mg of hyperforin. This means that no homeopathic medicine, even in low dilution, can cause enzymatic interference with hepatic cytochromes, confirming that homeopathy in supportive care is extremely safe.

13. Conclusion

Improving quality of life, facilitating tolerance and promoting therapeutic compliance are the three challenges to be overcome if we want the patient to fully benefit from the therapeutic efficacy of these new targeted therapies. By knowing the mechanism of action and the main side effects of these new treatments, it will be easier to anticipate them with organotherapy support and accompanying isotherapy. If symptoms occur, they are treated according to the principles of similarity and individualisation specific to homeopathic therapy in an integrative approach, that is

to say by adding to them conventional supportive care when necessary [31]. Finally, the sometimes difficult but essential choice of the constitutional medicine, specific to each patient, will make it possible to support the whole body, at a physical and psychological level. Clinical studies are now necessary to scientifically verify and evaluate the favourable clinical impressions felt by patients.

Author Contributions

The author did all the research work of this study.

Competing Interests

Bagot JL declares a specific activity of expert and scientific adviser for Boiron laboratories unrelated to this article.

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