

“Active home-based”: a new model for cancer treatment

“Active home-based”: un nuovo modello per il trattamento del cancro

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The advent of oral chemotherapy agents has had a strong impact on several aspects of the management of cancer patients, including survival rates, health-care expenditure, and health-related quality of life. The access to care and adherence to oral chemotherapy are central to optimal outcomes.

“Active home-based” cancer treatment is a new model of service before experienced as a pilot project and then as inter-institutional experience. This experience proposes that a home care given to terminally ill patients not receiving “palliative” patients but “actively maintained” with anticancer oral drugs, thus transferring the cancer care from the hospital to the patient’s home.

The Active home care program was associated with improvements in the quality of life of patients and caregivers, better adherence to treatment, and the effective management of therapy and cancer-related symptoms. Home-based cancer treatment may also optimize the utilization of health-care resources.

Key words: Chemotherapy, home-based care, quality of life

L'avvento di agenti chemioterapici per via orale ha avuto un forte impatto su diversi aspetti della gestione dei pazienti affetti da cancro, compresi i tassi di sopravvivenza, la spesa sanitaria, e la qualità della vita. L'accesso alle cure e l'adesione alla chemioterapia orale è fondamentale per ottenere risultati ottimali.

Il “Domicilio attivo” è un nuovo modello di servizio sperimentato prima come progetto pilota e poi come esperienza interistituzionale. Questa esperienza propone un'assistenza domiciliare rivolta non a malati terminali, che ricevono cure palliative, ma a pazienti oncologici in trattamento attivo con farmaci antitumorali somministrati per via orale, trasferendo così la cura del cancro dall'ospedale al domicilio del paziente.

Il progetto “Domicilio attivo” è stato associato con un miglioramento della qualità di vita dei pazienti e dei “caregivers”, una migliore aderenza al trattamento, e una gestione efficace della terapia e dei sintomi correlati al cancro. Questa modalità di assistenza può anche ottimizzare l'utilizzo delle risorse sanitarie.

Parole chiave: Chemioterapia, assistenza domiciliare, qualità della vita

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Oral chemotherapy

The last decade has witnessed an expansion and acceleration of the development of anticancer oral drugs, especially those of cytotoxic agents that interact with surface receptors of tumor cells or other molecules involved in processes that regulate cell proliferation in tumor cells, the so-called “biologics” or “targeted therapy”. The percentage of antineoplastic drugs administered orally is likely to grow. It was estimated that the percentage of antineoplastic drugs in the oral formulation will be increased to 25% in 2013, compared to 10% in 2008 and that 85% of these are “target therapy” (National Comprehensive Cancer Network, 2008). There are now over 50 *oral anticancer medications* (OAMs) approved by the Food and Drug Administration in 2013 (Geynisman, 2013). Through recent understanding of genetic, genomic, and molecular changes involved in tumor progression, many oral anticancer therapies have been developed to target abnormal proteins and signaling pathways specific to cancer cells. The advent of oral chemotherapy has had a strong impact on several aspects of the management of cancer patients, including survival rates, healthcare expenditure, and health-related quality of life (De Portu, 2010; Sanon, 2013; Camma, 2013). Current evidences show similar quality of life profile between oral and intravenous treatments, although anticancer oral therapy seems to be more convenient in terms of administration and reduced time lost for work or other activities (Banna, 2010). Most patients prefer anticancer oral therapy to intravenous treatment primarily for the convenience of a home-based therapy, although they require that the efficacy of oral therapy must be equivalent and toxicity not superior than those expected with the intravenous treatment (Liu, 1997). Other reasons included previous negative experience with iv administration and a lower access rate to the oncology service, resulting in a lesser impact on the economic and familial support and on the loss of working days both for patients and for familiars. Two thirds of patients required that the efficacy of *anticancer oral therapy* (AOT) had to be equivalent to iv one, with 70% and 74% of patients not willing to accept less response rate and duration of survival, respectively (Liu, 1997). To prefer AOT patients need to be fully informed about the efficacy and toxicity of the oral alternative to the iv treatment. Regarding the oncologist perspective, the main prejudice against AOT – i.e. anticancer agents are best given iv because this route is more effective and reliable than oral administration – has been overcome by the recent availability of oral agents with proven clinical efficacy, as well as convenience (O’Neill and Twelves, 2002). In a survey carried out in 2005 involving 96 US oncologists, more than 80% of them reported an increase in the use of oral agents in the last 2 years (Decision Resources Survey, 2005). The most common reasons for this change were: availability of highly targeted agents, publication of more data supporting the use of AOT, and expanded indications for

already existing oral therapies. In a survey on 93 Italian oncologists, 82% indicated a better expected compliance as an advantage of AOT over the iv treatment, as well as better tolerability (43%), good activity (26%) and pharmaco-economic profile (7%) (Collovà et al., 2009). Research has invested also in new oral agents corresponding to the counterparty administered iv. For example, are developing oral versions of drugs such as cisplatin, docetaxel and topotecan. Experts suggest that a market will exist for both versions, oral and intravenous administration of several antineoplastic drugs. The future prospects of pushing more and more towards a process of de-hospitalization of oncology and the advent of oral chemotherapy will surely give an essential contribution in this direction, providing the basis for new models of care. Regarding cost-effectiveness, current evidences are in favor of oral therapy, mainly due to reduced need of visits and/or day in hospital for the administration of the drug and/or the management of adverse events.

Adherence to treatment

In this context, access to care and adherence to them is crucial to achieve the therapeutic aim of a chronic indolent neoplastic disease. The efficacy of oral chemotherapy is largely dependent on patients’ adherence to the prescribed protocol (Partridge et al., 2002; Ruddy et al., 2009). In fact, self-administration may increase the likelihood of errors such as missing a dose, overdosing or taking a dose at the wrong time, which in turn may lead to reduced efficacy, increased toxicity and potential drug-drug interactions in patients taking other medications (Partridge et al., 2002; Van Leeuwen et al., 2013). Adherence rates for oral cancer therapy vary widely, ranging from less than 20% to 100% (Partridge et al., 2002), and non-adherence is known to be associated with greater use of healthcare resources and costs due to more frequent physician visits, higher hospitalization rates and longer hospital stays (Gebbia et al., 2012; Lebovits et al., 1990). Several factors may contribute to poor adherence, e.g. individual patient characteristics, features of the disease and the treatment regimen, and aspects of the medical care system (Ruddy et al., 2009). Adherence (compliance often called) can be defined as the extent to which a patient’s behavior coincides with the prescription (Haynes et al., 1979). The adherence to any treatment for long periods, is largely determined by the perception of individual risks, benefits and costs of intervention (Love et al., 1991). Adherence to treatment is a complex and multifaceted able to modify substantially the results of therapy (Tebbi, 1993).

Adherence to the prescribed dose of AOT is a particularly important issue for at least two reasons: treatment efficacy and toxicity are strongly dependent on correct drug assumption, and the ultimate determinant of compliance is the patient him/herself and not the physician or the nurse as for the iv admin-

istration. A poor adherence may cause a loss of treatment efficacy as the obvious consequence of the reduction of dose-intensity, as shown for adjuvant chemotherapy for breast cancer. This evidence comes from the updated results of the adjuvant CMF chemotherapy, that is a mixed oral and iv chemotherapy; patients receiving 85% or more of the optimal dose of this regimen showed better overall and progression-free survival compared to those receiving <85% of the optimal dose (Bonadonna et al., 1995). A similar observation in terms of increased risk of death was reported in breast cancer patients who had < 70% of the prescribed dose of tamoxifen (Thompson et al., 2007). In the metastatic setting of disease, compliance to AOT in terms of efficacy may be still important, since a suboptimal adherence to AOT may be associated with poor patient outcome. Access to treatment turns out to be more difficult with increasing age and often a high number of elderly patients at diagnosis is presented with a very advanced stage of disease that does not allow therapeutic procedures with curative intent. In a recent study investigating compliance to six cycles of Capecitabine by the use of *Micro-Electronic Monitoring Systems* (MEMS) on 161 patients with breast cancer, it was observed that only 76% of patients took at least 80% of doses (Partridge et al., 2008). Thus, a suboptimal adherence may be the greatest barrier to the effective use of AOT, particularly if the oncologists fail to consider this potential obstacle (Partridge et al., 2002). Several studies have suggested that poor adherence occurs more frequently than either patients or physicians recognize, contributes to poorer outcomes, and may contribute to increased health care costs (Noens et al., 2009; Ibrahim et al., 2011). The ADAGIO study (Noens et al., 2009) examined adherence in 169 patients in Belgium and observed that approximately one-third of patients were non-adherent and only 14.2% of patients were 100% adherent with prescribed IM. Non-adherence was associated with poorer cytogenetic response. Compliance to AOT may depend on several factors linked to treatment, including: the number of tablets to swallow every day, the complexity of the regimen and the related patient ability to follow the dosing schedule, and the duration of treatment (Findlay et al., 2008; Partridge et al., 2002). Simplification of complex schedules of AOT regimens is also important and should be attempted when possible to avoid that the oral regimen governs patient daily activities. Factors related to the interaction with system, include: the availability of the medical staff; the clarity and validity of the communication and information provided; an adequate social, psychological and caregiver support. However, patient education by physicians, nurses and other healthcare providers, as well as ease of access to healthcare, may substantially improve adherence (Osterberg and Blaschke, 2005) The treatment strategy should be set considering, among other factors, the actual life expectancy of the patient: it now subjects 65 years old may have a life expectancy of 21 years if women and 18 men, and that if a healthy person of 75 years still has 13 or 10 years if male or female, average life expectancy. Increases with increas-

ing age, in fact, not only the incidence of the disease cancer but also your overall comorbidity, and there is often found to co-exist with underlying conditions and / or disabilities that make it difficult to complete a treatment program. In fact, the need to take more drugs (comorbidities), the infrequent availability of home support full, the need for chronic therapy, often are risk factors for failure to complete the treatment program. Several methods may be used to assess compliance to AOT, though each has a potential barrier to an objective evaluation, and none is currently validated as a standard (pill counting, questionnaires, self-reporting etc...). Oral treatment requires a greater responsibility and control of the patient compared to parenteral treatment, whose adherence depends instead on the administration controlled by the physician. Patient-focused education and motivation by the oncologist, the psycho-oncologist, and the nurse, may allow to increase patients understanding of her/his disease, as well as of the risks and benefits of the treatment prescribed, and proper use of medications.

Chronicity, Qol and cost of oral care therapies and new paradigms

The chronicity of the tumor is large and growing phenomenon due to the success of the treatment, a greater number of drugs and reducing the time of diagnosis, which allows more effective therapeutic interventions. In recent years, thanks to the possibility of molecular targeted drugs and also a better understanding of the natural history of disease, the treatment goal has changed: not always trying to destroy, but rather inhibit the neoplastic population, probably for a long period, the cell replication in order to control the expansion of local and systemic, ultimately become chronic clinical expression. Knowledge of the natural history of disease and the development of standardized protocols in the different lines of chemotherapy treatment has allowed us to control the evolution of many neoplastic diseases, increasing the overall survival and disease free, in the early stages, the time to progression and remissions, in advanced stages. The survivals in patients with breast cancer, for example, have greatly increased thanks to the introduction of adjuvant chemotherapy protocols, an evolving field in which the different modes should be combined to improve outcomes and quality of life in these patients (Tsoutsou et al., 2010) and molecular targeted drugs like Trastuzumab, have profoundly changed the natural history of disease. So now you can live "long" and "better" with the tumor. Suffice to say that from 1971 to 2001, the number of cancer survivors in the United States has increased from 3.0 million to 9.8 million and tumors of the breast, prostate and colon-rectum are the most common types of cancer among the survivors, with 51% of the diagnoses (Centers for Disease Control and Prevention, 2011).

The goal of cancer care today, as well as to "cure" the patient is also to ensure a "better quality of life" of the same, for

a more rational and efficient management of the disease in its different phases. For example, “Living with cancer” and therefore control of the symptoms are the features and benefits of integrative medicine in the treatment of metastatic non-small cell (Xue and Li, 2001). The clinical benefit (CB) is designed as an endpoint widely understood and accepted in clinical trials in oncology. In patients with advanced cancer or metastatic spread of the possibilities for healing are scarce, however, often with a specific integrated multidisciplinary treatment and “cut” on the individual patient can become chronic disease and ensure the patient living with the disease and a good quality of life. The quality of life is a fundamental aspect of adherence to treatment. Current evidences about QoL for AOT are limited to colorectal cancer (Conroy et al., 2010; Twelves et al., 2006) and show similar QoL profile between oral and iv treatment, although AOT seems to be more convenient in terms of administration and reduced time lost for work or other activities compared to iv therapy.

Finally, the analysis of costs for AOT should include the cost comparison of oral alternatives to iv drugs, the resource saving, and the reimbursement system. In a French randomized phase III trial on patients with stage III colon cancer, oral Capecitabine was associated with savings of €7025 and €3569 per patient as compared with the iv Mayo Clinic and de Gramont regimens, respectively (Douillard et al., 2007). An Italian analysis confirmed that Capecitabine is the “dominant strategy” in pharmacoeconomic terms, with saving from the Italian hospital perspective of € 2,234 per patient (Di Costanzo et al., 2008). In general, AOT compared to iv treatment has the potential advantage to alleviate oncology staffing shortages, especially those of nurses and pharmacist, nevertheless the increase in the nursing and physician time required for ongoing patients education and support, such as answering telephone calls from patients receiving AOT.

The acquisition of new therapeutic possibilities offered by the advent of oral chemotherapy in oncology, self-administered directly by the patient at home, has resulted in the birth of new care needs. Self-administration of oral chemotherapy can be convenient for the fact that cancer patients can receive care at home rather than in a supervisory and control health care as the hospital. This new paradigm shifts the focus of care towards the patient becomes leasing of therapy and not just the recipient, although health care professionals to banishing the important function of the watchful care pathway (Bedell, 2003). This raises the need by the health care professionals, to monitor adherence to this new route of administration in perspective of an optimal therapeutic success and, by the patient, the need to deal with all issues related to ‘access to facilities cancer (involvement of family members, lost working hours, transport the elderly debilitated, the use of healthcare resources...). In the same direction, it seems imperative to find ways to support patients at home, particularly when oral chemotherapy is given to elderly and frail patients. A homecare nursing symptom-focused intervention for pa-

tients receiving Capecitabine appeared an effective way of supporting patients, decreasing symptom burden and leading to reduced service utilization (Molassiotis et al., 2009). This home-care nursing program included symptom assessment, patient education, and/or treatment of symptoms on the basis of agreed protocols. The key elements were one standard home visit during the first week of Capecitabine (often in the presence of family members/caregivers) and one monitoring phone call per week during all cycles. Subsequent home visits were offered when patients experienced multiple grade 3 toxicities or had difficulty coping with the chemotherapy (Molassiotis et al., 2009).

The experience of “Active home-based” cancer treatment

“Active home-based” cancer treatment is a new model of service before experienced as a pilot project and then as inter-institutional experience. This experience therefore proposes that a home care given to terminally ill patients not receiving “palliative” patients but “actively maintained” with anticancer oral drugs, thus transferring the cancer care from the hospital to the patient’s home. The first experience has been developed within the medical oncology unit of Syracuse between December 2009 and December 2010 selecting 30 cancer patients referred to this department (Bordonaro et al., 2012). In one year 321 accesses at home have been made. The oral treatment has been fully accepted and completed by all patients. The possibility of an Active Home Care has found all patients in agreement and satisfied. Voluntary withdrawals from chemotherapy was absent and all the patients carried out and completed the planned treatment. Patients with G3 and G4 toxicity received an adequate dose or a delay in treatment, but none of these stopped the treatment. Only 6 accesses have been made at the Hospital Oncology Unit with characteristics of emergency. It means that were avoided 98.% of access in the hospital (Fig. 1).

Accesses avoided in Hospital

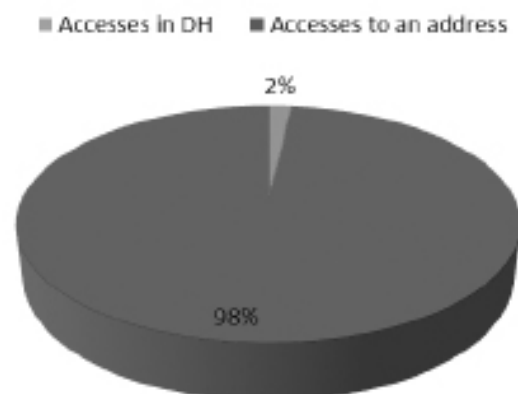


Figure 1. Accesses avoided in Hospital.

Coefficient's variability of quality of life over time

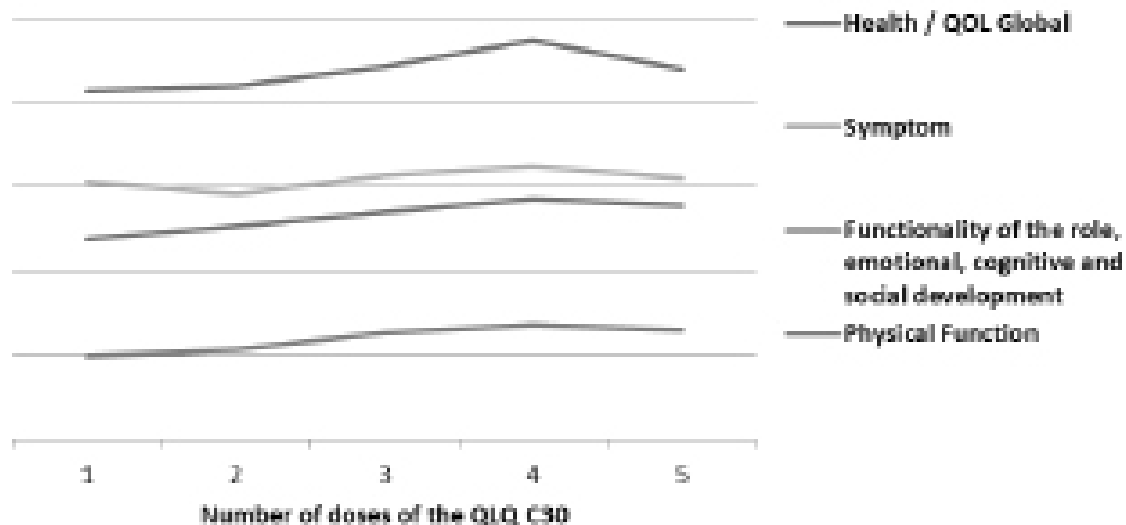


Figure 2. Variability of quality of life over time.

The project has promoted the quality of life of patients treated with oral chemotherapy (increase in all EORTC QLQ-C30 scores over time), allowing for greater adherence to oral treatment, through a real control of self-administration outside the hospital. The quality of life questionnaire (EORTC QLQ-C30 V 3.0) scores reported an improvement of symptoms, especially at the beginning and a better perception of health / global QoL over time (Bordonaro et al., 2012). (Fig. 2). These results are interesting considering the access barrier registered for all the patients enrolled.

Subsequently, the project was expanded to include other two cancer centers in Sicily (Ospedale "S. Giovanni di Dio", Agrigento, and Ospedale "S. Vincenzo", Taormina) between April 2012 and February 2013 (Bordonaro, et al. 2014). In the home-based cancer program offered by the participating centres, weekly home visits are scheduled with a trained nurse who delivers the home-based chemotherapy and reviews patients' compliance and treatment toxicity. An oncologist evaluates patients and modifies the dosage of oral chemotherapy based on toxicity during the previous cycle at bi-weekly visits conducted by the doctor personally at patients' home. Patient quality of life was measured at baseline and after three months or two chemotherapy cycles (whichever occurred first) using the 30-item European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire version 3.0 (Aaronson et al., 1993). Acceptability of oral chemotherapy was evaluated by a self-administered questionnaire specifically designed to identify the adherence to therapy and degree of satisfaction with oral chemotherapy, as compared with intravenous therapies. Sixty-two patients

(26 males) with a mean age of 67.8 years in a range of 33-83 years on oral chemotherapy were enrolled in the "Active Home Care" inter-institutional project. More than half of patients (56%) were 70 years of age or older. The patients were suffering from the most common neoplastic diseases (breast, colon, lung, renal, HCC, GIST, pancreas etc.) and were treated with anticancer drugs most often used in oral formulations (capecitabine, vinorelbine, imatinib, sunitinib, sorafenib, temozolomide, ibandronate). A total of 460 home visits were performed during the period considered. Only 9 hospital admissions were recorded. The Active Home Care initiative was associated with changes in EORTC QLQ-C30 scores. Significant improvements ($p < 0.05$) were seen in the symptom (fatigue, pain, nausea and vomiting) and physical functioning scales and in several individual items (dyspnoea, sleep disturbances, appetite loss and constipation) (Bordonaro et al., 2014) (Fig. 3).

Acceptability of oral chemotherapy was high. All patients considered the information received on the oral regimen to be complete and exhaustive, and thought that being on oral therapy was more advantageous as compared with being treated with intravenous therapies, both in terms of time saved (less time spent in hospital) and of having more time to spend with family and friends. Also, all patients thought that an oral regimen was more convenient, since no bulky infusion devices are involved. Sixty patients (96.7%) considered home monitoring of compliance to treatment, patient's health status and possible adverse events by a nurse and/or an oncologist to be useful. No patient reported difficulties in managing the oral regimen, and all of them re-

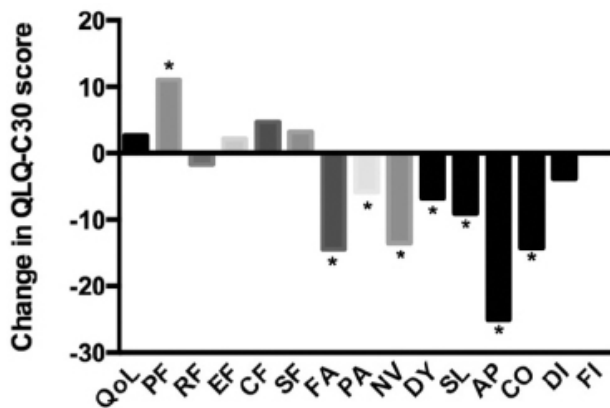


Figure 3. Mean change from baseline in the EORTC QLQ-C30 questionnaire after three months. * indicates significant difference from baseline ($p < 0.05$). QoL, global quality of life, PF physical functioning, RF role functioning, EF emotional functioning, CF cognitive functioning, SF social functioning, FA fatigue, PA pain, NV nausea and vomiting, DY dyspnoea, SL insomnia, AP appetite loss, CO constipation, DI diarrhoea, FI financial difficulties.

ported to have taken their medications according to the indications provided by the physician. The majority of patients (> 80%) would have needed to be accompanied to hospital visits by a family member or friend who, in most cases, had to take time off from work to do so. This is particularly true for elderly patients, since access to treatment becomes more difficult with advancing age due to increased disability. Reducing the number of hospital visits would reduce both direct and indirect costs for caregivers, who often cover the costs of transportation and, in most cases, have to take time off from work. In addition, among caregivers the overall satisfaction with the program was even higher than among patients. The “Active Home Care” initiative also decreased the number of visits to primary care physicians, which may result in reduced healthcare costs (Bordonaro et al., 2014). These findings are in accordance with previous studies showing that patients receiving home care had fewer visits to their general practitioner, reduced contact with other health services, and fewer inpatient days (Molassiotis et al., 2009), and that home-based care models are associated with lower costs than inpatient hospital care (Raphael et al., 2005).

Conclusions

The new achievements from research in oncology have provided a real chronic neoplastic disease. The advent of oral chemotherapies have offered the patient a real benefit, especially in terms of quality of life and paved the way for new types of assistance to cancer patients. The implementation of “Active Home-Based” cancer treatment has resulted in a noticeable improvement of the quality of life of patients treated with home oral chemotherapy, allowing the continuation of

the treatment program in a fully accepted and shared by both the patient and the family members who care for them. The project has significantly reduced the number of accesses to the hospital by the patient and their careers, resulting in an income reduction of both direct costs and indirect, thus affecting the cost-effectiveness of public spending. Ultimately it can be said that the project can be the starting point of a much broader discussion, which is part of a new home cancer care model where the nurse has a central role.

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