




Optimization of resources by drug management: A multicentred web-administered study on the use of ipilimumab in Italy

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Abstract

Objective: In a scenario of new expensive cancer therapies entering the market, strategies of optimisation and cost containment are crucial in oncology care. Better management of drug waste and centralization of drug preparation can be effective strategies to achieve these goals. The aim of this work is to describe the economic management of a high cost anticancer drug (ipilimumab) in some Italian reference centres.

Methods: This was an observational, multicentred study in which economical and clinical data of 21 cancer centres (418 patients) were collected during the enrollment period from February 2013 to August 2014. The follow-up period ended in July 2015.

Results: Participants purchased 10.7% more vials of ipilimumab than necessary for compounding. The results were variable among centres, and only five centres had a deviation lower than 5% between the drug purchased and the drug prescribed. Hospitals applying the *drug day* reached a statistically significant residual of drug effectively used compared to the amount prescribed ($P = 0.018$). Consequently, the price for treating a model patient was significantly lower in those hospitals (median spare of 7456 euro per patient).

Conclusions: This study demonstrated that the careful management of drug waste and the application of *drug-day*, through a proper selection of vial and the ability to use the leftover drug, can generate economic savings. However, tailoring the drug stock to clinical need is still an open issue which deserves further analysis.

Keywords

Drug compounding, ipilimumab, melanoma, vial-sharing, sustainability

Date received: 17 October 2017; revised: 2 January 2018; accepted: 7 January 2018

Introduction

The incidence of malignant melanoma is constantly increasing. In 2015, a global age-standardized incidence rate has been estimated in 5 cases per 100,000 persons.¹ In recent years, novel drugs for melanoma have provided a significant advantage in survival over classic chemotherapy, especially for immunotherapy-treated

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patients, achieving long-lasting results in terms of overall survival.² Ipilimumab was the first immunotherapeutic drug that demonstrated a survival benefit over the long-standing standard therapy with dacarbazine in advanced melanoma.³

Costs associated with cutaneous melanoma have been extensively discussed and reviewed in literature,^{4,5} but new scenarios are opening up because the new immunotherapeutic drugs are very expensive treatments and are likely to cause an increasing economic impact on public and private healthcare systems.^{6,7} Moreover, ipilimumab requires a personalized dose based on the patient's body weight; as the amount of drug included in the vial rarely matches patients' weight, any unused residual amount is wasted. Opinions on standardized procedures to use leftovers are conflicting, but everyone agrees that vials should be handled safely and only in authorized pharmacies equipped with an aseptic chamber.^{8,9} Centralised compounding permits implementation of optimization processes that avoid waste and thus contains costs, especially for drugs with customized dosages and preservative-free vials such as ipilimumab.^{10,11}

Several methods have been designed to reduce waste and increase the efficiency of cancer drug compounding.^{9,12-14} For example, treatment administration based on a per-pathology and/or per-drug schedule (*drug-day*) can provide a significant decrease in drug waste costs.¹⁰ Centralization of drug compounding, dose banding, *drug-day*, and other organizational methods has clearly demonstrated their effectiveness, but high standards must be maintained through a nation-wide quality by design approach.

The Italian Ministry of Health has recently published a recommendation advising cancer centres to centralize the compounding of therapies in order to prevent the hazard of errors in therapy.¹⁵ Despite this recommendation, the management of expensive cancer drugs with custom dosages, such as ipilimumab, still varies consistently among cancer centres.

Our study aims to investigate the economic management of cancer drugs in terms of savings related to the reduction of waste during drug compounding in several Italian cancer centres. Ipilimumab for advanced melanoma is a perfect context to investigate this topic because it is an expensive drug, compounded with personalized doses, and only prescribed in authorized hospitals.

Materials and methods

Design of the study

The study was prospective, observational, multicentre, and it was performed using a web-based community of oncology pharmacists (Oncofarma).¹⁶

The study aims to investigate the economic management of ipilimumab. This drug was chosen because it is the first drug producing a significant longer survival in melanoma patients thanks to an innovative mechanism of action. The novelty of ipilimumab comes with an extremely high cost. To balance between extreme efficacy and high cost, some restrictions have been posed to ipilimumab prescription. Indeed, ipilimumab can be prescribed only in hub centres and prescriptions are monitored through a National web-based Registry.

Participation in the study was voluntary; 122 cancer centres expressed the intention to join the project but only 21 were considered eligible. Reasons for failed inclusion were: (1) the centre was not a hub-centre authorised to prescribe ipilimumab (n=11), (2) the centre was an authorised prescribing centre but did not have the intention to treat patients with ipilimumab (n=15), (3) the centre was eligible, but it was lost to follow-up (n=75).

A hospital pharmacist and a clinical oncologist for each centre were involved as study investigators. Each participating centre could choose whether to share clinical data of efficacy and safety of ipilimumab and/or administrative data about consumption. Administrative data were: number and type of ipilimumab vials purchased and used for compounding. Clinical data included: information about treatment (number of patients treated, individual dose, no. of drug cycles received, body weight, patient demographics), efficacy (time to progression and/or overall survival, best overall response), and toxicity (type, grade and number of adverse drug reactions). Clinical data and analyses of overall survival, progression-free survival and toxicity have been published in a previous work.¹⁷

The study was approved by the Ethics Committee of the coordinating centre (Veneto Institute of Oncology), and each participant hospital provided a notification to the local Ethics Committees.

Patients

Patients with metastatic or locally advanced, non resectable melanoma who had previously received at least one line of chemotherapy and afterwards were treated with ipilimumab were considered eligible for the study. Patients must have an ECOG (Eastern Cooperative Oncology Group) performance status equal to or lower than 2 and no symptomatic brain metastasis. Patients enrolled in clinical trials or on compassionate use (expanded access) programs were excluded. Patient received ipilimumab 3 mg/kg for four cycles and could stop therapy in case of disease progression or intolerable toxicity.

Data collection

Clinical and pharmaceutical data were collected during the enrollment period from February 2013 (first approval date of ipilimumab in Italy) to July 2015.

We collected information about the number and type (200 mg/40 mL or 50 mg/10 mL) of ipilimumab vials purchased, actually used for compounding and the amount (in mg) of ipilimumab administered to each patient in each treatment cycle. We also recorded the body weight of patients and the number of treatment cycles administered.

We asked investigators whether they apply *vial sharing/drug-day* procedure in their hospital for ipilimumab compounding and administration. *Drug-day* is applied when all treatments with ipilimumab were administered (and compounded) on the same of day of the week, following an every three-week schedule. In the *vial sharing* procedure, the properly stored leftover of a vial is used for the compounding to the next patient.

For economic evaluation, we considered ex-factory price of ipilimumab.¹⁸

Statistical analysis

Continuous variables were described using the median and interquartile range and minimum and maximum, when required. Categorical data were expressed as frequencies.

To compare the amount of ipilimumab purchased or used for compounding between centres, we normalised data on the amount of ipilimumab prescribed in each centre. For calculation, we considered the amounts in milligrams and we expressed the amount of ipilimumab prescribed or purchased as fraction of the amount prescribed within each centre.

Deviation between milligrams of ipilimumab purchased and prescribed (ΔPP) was calculated as follows: (mg purchased–mg prescribed)/mg prescribed.

Deviation between milligrams of ipilimumab used for compounding and prescribed (ΔUP) was calculated as follows: (mg used–mg prescribed)/mg prescribed.

To compare the cost of treatment in centres, we considered a model patient who had a body weight equal to the median body weight of the cohort and received the median number of cycles ($n = 4$).

Boxes represent the 25th to 75th percentile of data, mean is represented as a dot, and median is represented as a line dividing the box. Comparison between medians was done using the Wilcoxon Rank Sum Test, and the difference is considered statistically significant for $P < 0.05$.

Overall Survival (OS) was calculated according to the Kaplan Meier method, and comparison between survival times of different groups was performed by Log Rank test.

Results

A total of 21 Italian cancer centres participated in the study, collectively enrolling 418 patients. The median number of patients treated per centre was 15, but considerable variability between centres was recorded (IQR: 4.5–30.5, min = 1, max = 66 patients).

Management of drug supply

The compounding of ipilimumab therapies was performed using vials containing 200 mg/40 mL (78.6% of total number of vials bought), while only 21.4% of the purchased vials corresponded to smaller vials containing 50 mg/10 mL. Most participants used both vial sizes; only two hospitals chose the smaller size vials. Figure 1(a) shows the percentage of vials for each size.

Figure 1(b) reports, for each participant (ID), the ratio between the milligrams of ipilimumab purchased and prescribed (ΔPP). Participants had a median ΔPP of 10.7%; the deviation was lower than 5% in five centres (24%), between 5 and 10% in five centres (24%), between 10 and 15% in seven centres (33%) and above the 15% for four centres (19%).

Evaluation of efficiency of vial use

Figure 2(a) represents the ratio between the milligrams effectively used for compounding and prescribed (ΔUP). ΔUP is highly variable between centres; Nine out of 21 centres have a negative deviation, while a similar number of participants presented high deviation, even above 10%

Three out of 21 centres applied the *drug-day* procedure. These were big cancer centres that enrolled 115 patients in the study. Hospitals applying the *drug-day* had a significantly lower ΔUP compared to participants that did not apply this rationalisation strategy (4.1% no *drug-day* vs. –5.9% with *drug-day*, $P = 0.018$, Figure 2(b)).

When ipilimumab was administered in a single day, the price for treating a model patient was significantly lower than in hospitals not using the optimisation procedure, with a median savings of 7456 euro per model patient (Figure 2(c)). The money saved with *drug-day* permitted one free treatment every 9.4 treated patients, considering the model patient. This optimisation of resources came without any difference in survival (data not shown).

Discussion

This study was designed to estimate the economic impact of ipilimumab in real-practice because this drug entered the Italian market with an extremely

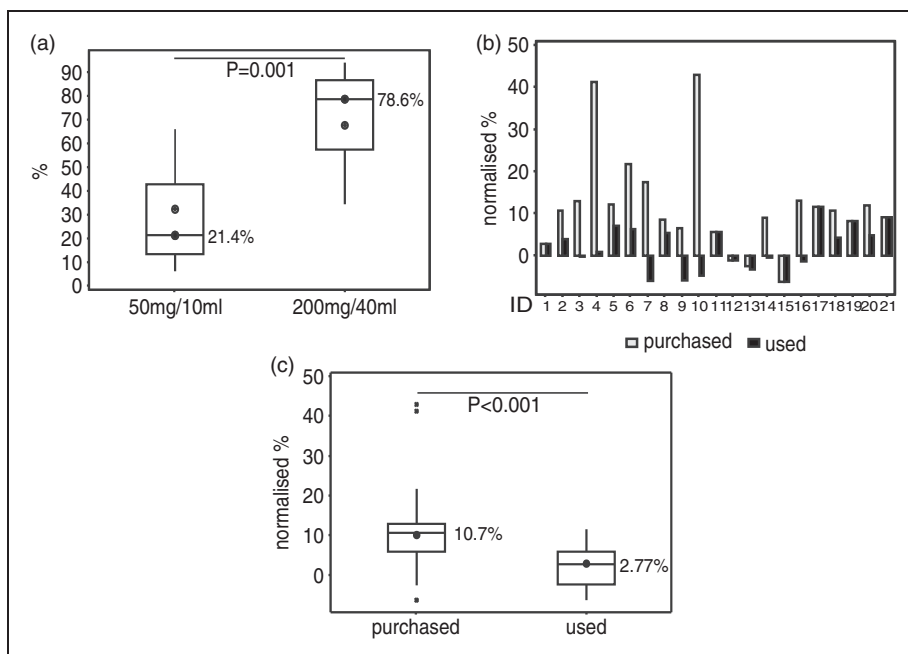


Figure 1. Management of drug supply. (a) The percentage of vials for each size. (b) for each participant (ID), the ratio between the milligrams of ipilimumab purchased and prescribed (grey bars) and the ratio between the milligrams effectively used for compounding and prescribed (black bars). The percentages reported are normalised on the number of milligrams prescribed. Median frequencies of purchased/prescribed milligrams and used/prescribed milligrams are reported in the box plot of panel C. Boxes represent the 25th to 75th percentile of data, mean is represented as a dot, and median is represented as a line dividing the box. Comparison between medians was done using the Wilcoxon Rank Sum Test and the difference is considered statistically significant for $P < 0.05$.

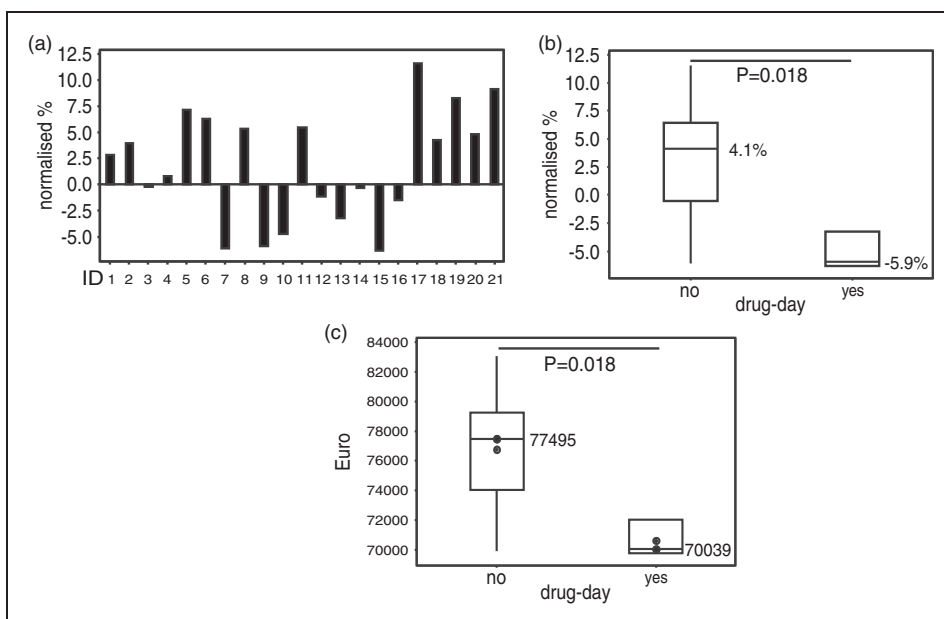


Figure 2. Evaluation of efficiency of vial use. (a) For each participant (ID), deviation between the amount of ipilimumab prescribed and actually used for compounding (ΔUP). This deviation is expressed as percentage normalised on the prescribed amount. Median deviations are reported (b) dividing the participants into who used the *drug-day* for optimization of resources and who did not. Boxes represent the 25th to 75th percentile of data, mean is represented as a dot, median is represented as a line dividing the box. Comparison between medians was done using the Wilcoxon Rank Sum Test and the difference is considered statistically significant for $P < 0.05$. (c) The cost for treating a model patient in hospitals which adopted and those that did not adopt the *drug-day*.

high price compared to other cancer treatments. The multicentered design of the study portrays a reliable picture of the Italian reality because we enrolled both hub and spoke hospitals taking care of both a high and low number of patients.

First, we recorded that hospitals prefer using 200 mg vials rather than 50 mg vials, regardless of the dimension of the hospital. However, this choice does not produce an economic advantage as demonstrated by Bach et al.⁸ They investigated the overspending driven by oversized single dose vials and found a significant mismatch between the size of the ipilimumab vial and the typical patient dose (210 mg). We confirmed that the typical patient dose considered in the study by Bach is reliable and similar to our cohort of more than 400 real-practice patients. As reported in Bach's study, the 7% leftover produced by the size of the ipilimumab vial is lower than other drugs such as bortezomib or carfilzomib, whose vial size resulted in up to 33% of leftover drug.⁸ Still, the extremely high cost of ipilimumab translates this discrete percentage into a high monetary value. Bach proposed adding a 10 mg vial and calculated that this would reduce the estimated waste from 46 to 10 million dollars per year. The correct estimation of vial size and cost is currently a hot topic in pharmacoeconomics and different methods for estimation of treatment cost have recently been compared in an interesting study by Hatswell et al.¹⁹

Another important issue for management of expensive cancer drugs is to tailor the stock to the clinical need of the drugs. We observed that only a minority of the hospitals have an ipilimumab stock consistent with the amount consumed to compound therapies. This discrepancy should be better managed also considering that ipilimumab is only used for a limited number of patients and with a fixed four-cycle schedule. A frequent communication between pharmacist and clinical oncologist, who should share information about the monthly plan of treatments, may reduce the discrepancy.

The schedule of treatment with ipilimumab and its long physiochemical stability makes it a model drug to investigate the effect of rationalisation strategy such as vial sharing and *drug-day*. Indeed, the fixed drug schedule permits planning of treatment and application of *drug-day*. These strategies significantly reduced the amount of leftover drug and the associated costs.

We acknowledge that our work presents limitations and the application of *drug-day* is only possible in hub centres, but not in smaller hospitals. Smith et al. recently estimated that one day vial sharing is still the best economic choice either in the case of a lower stability drug or in the case of drugs used for treatment in a smaller number of patients, such as ipilimumab.¹² Alternative strategies that are currently

entering the clinical practice (such as in USA) are the administration of flat doses instead of body weight adjusted doses as proven for nivolumab 240 mg over a biweekly schedule, which has a predicted efficacy and safety profile similar to the 3 mg/kg q2w schedule currently in use in Europe.²⁰ However, flat dosages are generally greater than the median doses required on the basis of body weight and therefore the patient may receive more biologic drug than needed. For this reason, regulatory agencies should ask the producer to rebate the prices of flat-dose products, already on the market, considering the lack of savings recovered by personalised drug doses.

Conclusion

This work is, to the best of our knowledge, the first study describing the convenience of procedures like *vial sharing* and *drug-day* through analysis of real-practice data and not by estimation on the amount of drug consumed in the previous years. This study demonstrated that the careful management of drug waste can be obtained not only by *vial sharing* but also by a proper selection of vial size. An aspect that deserves further analysis is the collaboration between pharmacists and physicians which may favour the tailoring the drug stock to clinical need.

Acknowledgements

Listed here are the representatives (pharmacist and physician) of each centre who collaborated in this project: Azienda U.S.L., Piacenza: Dr. A.Riva; Dr. L. Cavanna; IRCCS, Aviano: Dr. S. Cecco; Dr. A. Freschi; Ospedale "Mariano Santo", Cosenza: Dr. C. Oriolo; Dr. R. De Simone; IRCCS, Candiolo: Dr. F. Goffredo; Dr. M. Aglietta; IRCCS, Meldola: Dr. V. Di Iorio; Dr. L. Ridolfi; IRCCS-Ospedale San Raffaele s.r.l., Milano: Dr. M. Corti; Dr. A. Bulotta; Azienda Ospedaliero-Universitaria Policlinico S.Orsola-Malpighi di Bologna: Dr. C. Bertipaglia; Dr. B. Melotti; Istituto Nazionale Tumori, Milano: Dr. E. Togliardi; Dr. L. Di Giardo; Ospedale Santa Chiara, Trento: Dr. A. Pasqualini; Dr. S. Brugnara; Policlinico "Gemelli", Roma: Dr. E. Manca; Dr. A. Strippoli; A.S.L. Lanciano Vasto Chieti: Dr. D. Antonelli; Dr. P. Cioffi; IRCCS San Martino, Genova: Dr. B. Rebesco; Dr. F. Trovato; Ospedale Careggi, Firenze: Dr. R. Banfi; Dr. M. Vaiani; Ospedale Humanitas, Milano: Dr. M. Fazio; Dr.M.C. Tronconi; IRCCS G. Paolo II, Bari: Dr. P. Nardulli; Dr. M. Guida; Azienda Ospedaliero-Universitaria, Parma: Dr. S.Bologna; Dr. F. Leonardi; Ospedale di Senigallia: Dr. R. Mancini; Dr. F. Freddari; A.O. Papa Giovanni XXIII, Bergamo: Dr. F. Gregis; Dr. S. Nozza, Dr. M. Mandalà; Azienda Ospedaliero Universitaria Pisana: Dr. L. Dal Canto; ASO S.Croce e Carle, Cuneo: Dr. E. Grande; Dr. M. Ocelli; Azienda Ospedaliero Universitaria, Ferrara: Dr. Stella Sferra; Dr. A. Frassoldati; Ospedale di Cosenza: Dr. A. Sorrentino; Dr. G. Filippelli.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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