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Original Research

Switch to anti-programmed cell death protein 1 (anti-PD-1) fixed-dose regimen: What is the economic impact?

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Abstract ***Background:*** Nivolumab and pembrolizumab were initially developed using weight-based regimen doses. Recently, fixed-dose regimens were commercialised with reference weights higher than the accurate weight of patients with cancer in routine practice. This may have important economic consequences for healthcare systems.
Material and methods: Budget impact analysis was performed using real-world data both from Gustave Roussy database and the French National Hospital Discharge database and including patients treated with either nivolumab or pembrolizumab at Gustave Roussy and in France before the approval of fixed-dosing regimens in Europe. Main outcome is the expected annual budget impact of fixed-dosing regimens in France.
Results: From January to April 2018, 978 perfusions of anti–programmed cell death protein 1 were administered at our institution including 560 perfusions of nivolumab in 103 patients and 418 perfusions of pembrolizumab in 125 patients mainly treated for lung cancer and melanoma. The mean extra cost attributable to flat doses would have amounted to €284 (95% confidence interval [CI]: 241–327) per infusion of nivolumab and to €1287 (95% CI: 1200–1373) per infusion of pembrolizumab. Annually, at Gustave Roussy, it would represent an extra cost of € 477 120 (95% CI: 404 880–549 360) and €1 613 898 (95% CI: 1 504 800–1 721 742), respectively, for the year 2018. At the French national level, the expected annual budget impact is estimated at €55 162 211 for the year 2017.

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Conclusions: Weight references for fixed-dose regimens do not reflect the accurate mean weight of patients under cancer treatment and are likely to have substantial economic impact for healthcare systems.

1. Introduction

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1/PD-L1 pathway) are revolutionising the survival of a large number of patients with cancer. Among the ICIs currently available in the United States (US) and in Europe, two monoclonal antibodies, nivolumab and pembrolizumab, are widely prescribed.

The first randomised studies of nivolumab and pembrolizumab were conducted using weight-based regimens. These drugs were approved in various indications at the dose of 3 mg/kg every 2 weeks for nivolumab and 2 mg/kg every 3 weeks for pembrolizumab [1–3]. More recently, studies [4,5] were conducted using fixed-dose regimens on the basis of previous early clinical trials [6] or pharmacokinetic data [7], suggesting no difference in comparison with a weight-based dose regimen. Therefore, nivolumab is now approved in the US and in Europe at the dose of 240/480 mg every 2/4 weeks, which is the former dose for a patient of 80 kg, while pembrolizumab is approved at the dose of 200 mg every 3 weeks, corresponding to the former dose for a patient of 100 kg.

Here, we report the results of a budget impact analysis using real-life data in a European country before the transition to fixed dosing.

2. Materials and methods

From January to April 2018 (i.e. before the approval of fixed-dosing regimens in Europe), we looked at all the patients at our institution who were, for any type of cancer, treated with either nivolumab or pembrolizumab based on their weight. We analysed the actual dose received in mg per kg and the difference with fixed-dose regiment for each drug. Then, we compared the difference between the cost of their treatment in mg/kg and the expected cost of treatment if they had been treated with fixed dosing, assuming a constant price both for nivolumab and pembrolizumab. To estimate the annual budget impact of fixed dosing, we extrapolated the number of perfusions during the first 4 months of 2018 to the whole year considering constant activity. For the drug price, we used the official price published by the French Ministry of Health. We used the French National Health Insurance perspective.

To consolidate our results for Gustave Roussy and to evaluate the budget impact of fixed dosing at the national level, we used data from the French National Hospital Discharge database for the year 2017 before the switch to fixed-dose regimens. We selected all the patients treated with either nivolumab or pembrolizumab in 2017.

3. Results

From January to April 2018, 978 perfusions of anti–PD-1 were administered at our institution including 560 perfusions of nivolumab in 103 patients with mainly lung cancer (n = 55), melanoma (n = 23) and kidney cancer (n = 15) (Table 1). There were 418 perfusions of pembrolizumab in 125 patients with mainly melanoma (n = 87) and lung cancer (n = 32). The mean weight of patients treated with nivolumab was 71 kg (standard deviation [SD]: 16), and the

Table 1
Expected annual budget impact of flat-fixed dosing regimens of immune checkpoint inhibitors at Gustave Roussy.

Data	Nivolumab	Pembrolizumab
Number of perfusions (January–April 2018)[a]	560	418
Average dose in mg (95% CI)	213 (209–217)	152 (149–55)
Extra cost per perfusion (95% CI)	€284 (241–327)	€1287 (1200–1373)
Expected budget impact for 2018 (95% CI)[c]	**€477 120 (404 880–549 360)**	**€1 613 898 (1 504 800–1721 742)**
Number of perfusions in 2017[b]	1414	868
Average dose in mg (95% CI)	212 (209–215)	149 (147–152)
Extra cost per perfusion (95% CI)	€296 (263–323)	€1368 (1 2883–1 410422)
Expected budget impact for 2017 (95% CI[d])	**€418 544 (371 882–456 722)**	**€1 187 424 (1 113 644–1223 880)**

CI, confidence interval.
[a] Data source: Gustave Roussy pharmaceutical database.
[b] Data source: French National Hospital Discharge database.
[c] The number of perfusions over a 4-month period was extrapolated to a year. The CI of the budget impact is obtained multiplying the CI limits of the mean extra cost per perfusion by the extrapolated number of perfusions.
[d] The CI of the budget impact is obtained multiplying the CI limits of the mean extra cost per perfusion by the number of perfusions in 2017.

average dose per mg administered to patients was 213 mg (95% confidence interval [CI]: 209–217). The mean extra cost attributable to flat-fixed dosing would have amounted to €284 (95% CI: 241–327) per infusion of nivolumab and to € 477 120 (95% CI: 404 880–549 360) for all the patients treated at Gustave Roussy during a year (i.e. an increase of 13%). The mean weight of patients treated with pembrolizumab was 76 kg (SD: 16), and the average dose per mg administered to patients was 152 mg (95% CI: 149–155). The mean extra cost attributable to flat-fixed dosing would have been €1287 (95% CI: 1200–1373) per infusion of pembrolizumab and €1 613 898 (95% CI: 1 504 800–1721 742) per year for the patients treated at our institution (i.e. 32% increase). This extra cost is solely driven by the difference between the actual average weight of the patients on treatment and the theoretical weight chosen for fixed-dose regimens. Estimates obtained for the year 2017 using data from the French National Hospital Discharge database were consistent with the 2018 estimates at Gustave Roussy (Table 2).

At the national level, for the year 2017, the average dose per mg of nivolumab perfusion was 207 mg (95% CI: 206–207) resulting in a mean extra cost attributable to flat-fixed dosing of €349 (95% CI: 345–354) per infusion of nivolumab. The expected annual budget impact of flat-fixed dosing of nivolumab is estimated at €34 269 357 (95% CI: 33 876 585–34 760 322) which represents an annual increase of 16%. Similarly, the average dose per mg of pembrolizumab administered to patients was 154 mg (95% CI: 153–155), resulting in a mean extra cost attributable to flat-fixed dosing of € 1234 (95% CI: 1203–1250) per infusion of pembrolizumab and €20 892 854 (95% CI: 20 367 993–21 163 750) for all the patients treated in France during a year (+30%). In total, the expected annual budget impact is estimated at €55 162 211 (+19%) at the national level for the year 2017.

Table 2
Expected annual budget impact of flat-fixed dosing regimens of immune checkpoint inhibitors in France.

Data	Nivolumab	Pembrolizumab
Number of perfusions in 2017[a]	98 193	16 931
Average dose in mg (95% CI)	207 (206–207)	154 (153–155)
Extra cost per perfusion (95% CI)	€349 (345–354)	€1234 (1203–1250)
Expected budget impact for the year 2017 (95% CI)[b]	**€34 269 357 (33 876 585–34 760 322)**	**€ 20 892 854 (20 367 993–21 163 750)**

CI, confidence interval.
[a] Data source: French National Hospital Discharge database.
[b] The CI of the budget impact is obtained multiplying the CI limits of the mean extra cost per perfusion by the number of perfusions in 2017.

4. Discussion

Our study is the first to provide an estimate of the budgetary impact of switching to a fixed anti–PD-1 flat dose using real data in France. Results show that weight references for fixed-dose regimens do not reflect the accurate mean weight of patients under cancer treatment. In the US, the financial implications of shifting from weight-based to fixed-dose regimens have been raised [8,9]. Goldstein *et al.* [8] raised the issue of using unnecessarily high dose of pembrolizumab. Indeed, although it seems that there is no difference between weight-based dosing and fixed dosing in terms of efficacy and tolerance, the authors showed that adopting fixed dosing would result in an increase in the drug administration cost of US $0.825 billion at the national level. Based on sensitivity analysis, patients' weight was the second most important cost driver, given the fact that average weight in overall population might be different that actual average weight of patients under cancer treatment. The cost issue might be even more sensitive in other countries where the prevalence of obesity is lower. Indeed, while the mean weight in the US is 82 kg [10], it is significantly lower in Europe with an average weight of 72 kg [11].

4.1. Limitations

Shifting to fixed-dose regimens may have potential positive effects that we did not consider. Indeed, fixed dosing is expected to reduce both preparation time and product waste by providing the ability to administer the treatment to another patient when he/she is unable to receive it. Fixed dosing may also diminish the potential risk of a wrong prescription. Another limitation is that we only considered doses in mg per kg in patients treated at Gustave Roussy without evaluating the total amount of vials actually used. Consequently, we might miss the potential losses when a vial is opened and not used entirely. Nonetheless, the losses are expected to be very limited, given the high volume of our day hospital offering the possibility to prepare the treatment of a patient from different vials, thus limiting the risk of waste. Finally, our estimation might underestimate the overall budget impact of ICIs because the number of indications of ICIs rapidly increases.

5. Conclusions

Our findings demonstrate that fixed dosing is likely to have substantial economic impact at the nationwide for the French National Health Insurance. This issue, that will also affect other countries [12,13], must be addressed urgently by health authorities in order to adjust the price accordingly to this change of practice.

Author contributions

Benjamin Besse, Arnaud Bayle and Julia Bonastre contributed to study concept and design and drafting of the manuscript. Arnaud Bayle and Julia Bonastre helped in acquisition, analysis or interpretation of data. All authors participated in revision of the manuscript. Arnaud Bayle helped in statistical analysis. Julia Bonastre and Benjamin Besse participated in study supervision.

Conflict of interest statement

Benjamin Besse: Sponsored Research at Gustave Roussy Cancer Center: Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda and Tiziana Pharma. Julia Bonastre: BMS: Travel for attending to Congress, consulting fees; MSD: consulting fees. The other authors declare that they have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.02.016.

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