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How to use busulfan in conditioning for allogeneic transplantation

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Summary

Busulfan-based conditioning has been used for decades in allogeneic haematopoietic stem cell transplantation (allo-HSCT). Initially, the drug was given orally. However, variable absorption rates from the gut resulted sometimes in adverse toxic effects. Later on, intravenous administration has replaced oral administration, but many centres still use the oral route. Moreover, different centres use various administration schedules and pharmacokinetic assays to individualize busulfan dosage. A Working Party of the European Society for Blood and Marrow Transplantation (EBMT) has carried out a survey among EBMT centres about their practice in the use of busulfan for conditioning in HSCT in adults, including dosage and routes of busulfan administration, and role of pharmacokinetic monitoring. At most centres, busulfan is given intravenously, both in myeloablative and reduced-intensity conditioning. There is marked variation between centres in the details of busulfan administration. The clinical impact of this variation remains uncertain. Efforts toward a more standardized use of busulfan in the conditioning would be indicated.

Keywords

Busulfan, hematopoietic stem cell transplantation, administration route, dosage, monitoring.

Introduction

Busulfan-based conditioning in various combinations is widely used in allogeneic haematopoietic stem cell transplantation. Busulfan was initially given orally in myeloablative doses. Erratic absorption from the gut and thereby variable bioavailability resulted in deviations from the target exposure to the drug, causing sometimes undue organ toxicity. Therefore many centres began to adjust the doses based on pharmacokinetic measurements. With the introduction of an intravenous (i.v.) formulation, options for the administration were increased. Intravenous administration has widely replaced oral administration, but many centres continue to use the oral route. The role of pharmacokinetic measurements, particularly in i.v. administration, remains unclear. The practice of busulfan administration for conditioning at transplant centres is evidently heterogenic, and details in which the policies of centres are likely to differ include the route of administration, number of daily doses, use of pharmacokinetic measurements, and adjustment of doses based on obesity. The possible impact of such differences on the outcome is unknown.

Doses and administration of busulfan in conditioning

The classical total dose in myeloablative conditioning is 16 mg/kg orally (or the corresponding dose calculated per m^2). The equivalent i.v. dose is 12.8 mg/kg. In recent years, lower doses have been widely used in the so called reduced intensity conditioning (RIC). In RIC, the dose has most commonly been 8 mg/kg orally or the equivalent i.v. dose of 6.4 mg/kg. However, especially with i.v. dosing the RIC doses have varied to some extent.

The two administration routes have their advantages and disadvantages. Oral busulfan administration was the routine for a couple of decades. However, it is characterized by variable absorption from the gut and the risk of increased toxicity in case of high absorption. Moreover, the oral administration route is inconvenient. On the other hand, this drug form is inexpensive. Intravenous infusion avoids absorption variability from the gut and first pass liver metabolism, thus allowing a more precise dosing and easy administration. However, this formulation is rather costly.

Oral administration of conventional fully intensive doses is traditionally performed in four daily doses, 1 mg/kg x 4/day, for 4 consecutive days. There are practical reasons for splitting the daily doses. Large numbers of tablets (usually 2 mg/tablet) have to be taken, and gastrointestinal irritation and vomiting may complicate the administration. In early studies of i.v. administration, four daily doses were given according to the classical schedule. Later studies have shown that the daily i.v. dose can be given in one dose without adverse consequences. Pharmacokinetic parameters have been shown to be similar with once daily and four times daily schedules [1]. The only difference was a higher peak concentration with the once daily schedule. However, the higher peak concentration did not cause any additional toxicity. Therefore, the present evidence suggests that the daily i.v. dose can be given safely in one dose.

What is the role of pharmacokinetic monitoring for dose adjustment?

Because of variable absorption of busulfan in oral administration, many centres adopted pharmacokinetic monitoring for dose adjustment although the necessity was not uniformly accepted. In i.v. administration with more precise dosing, the role of pharmacokinetic monitoring is still more unclear. In addition to the unclear indications, there may be practical problems with the use of pharmacokinetics. In many institutions the methodology is not available, and especially in RIC with a short schedule there may also be problems in getting the laboratory results in time.

The busulfan metabolism in children differs to some extent from that of adults. The use of busulfan conditioning or the role of pharmacokinetic measurements in paediatric patients are not discussed in this presentation.

Current practice

The Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation (EBMT) has carried out a survey among EBMT centres about their practice in the use of busulfan for conditioning in allogeneic transplantation in adults [2]. One hundred and nine centres sent their reports. Of these, 104 used busulfan for conditioning, 102 in conventional myeloablative doses and 87 in reduced doses. Both myeloablative and reduced doses of busulfan were used in a wide variation of diseases, including myeloid and lymphatic leukaemias, myelodysplastic and myeloproliferative disorders, lymphomas, myeloma, haemoglobinopathies and other inherited disorders.

When myeloablative doses were used, the drug was given i.v. in 90 and orally in 11 centres. In RIC with lower busulfan doses, the route of administration was intravenous in 73 and oral in 10 centres.

Myeloablative oral doses were always given on four days, on each day four doses of 1 mg/kg. In i.v. administration, the myeloablative total dose was most commonly approximately 12.8 mg/kg. Myeloablative i.v. doses were always administered in four days. The number of daily doses was one in 44 centres, two in 4 centres and four in 40 centres.

In RIC transplantations, the most common policy was to reduce the number of days from that used in myeloablative conditioning, whereas the daily dose and the administration schedule remained the same. The number of daily busulfan doses in RIC transplantations was one in 33 centres and four in 28 centres.

Seven centres determined the busulfan dose based on body surface area, the rest (97 centres) based on weight.

Overall, 16 of the 104 centres used pharmacokinetic measurements for dose adjustment in myeloablative conditioning, 9 of these also in RIC. There was no difference between centres giving oral or i.v. busulfan in the use of pharmacokinetics for dose adjustment, in full dose conditioning 3/11 vs. 14/90 centres, respectively. In RIC transplantations, pharmacokinetic-based dose adjustment was used in 1/10 centres giving oral busulfan and 8/73 using i.v. busulfan.

Busulfan concentration was measured with liquid chromatography and mass spectrometry in 7 centres, in the remaining ones with liquid chromatography. The parameter used for dose adjustment was area under the curve (AUC) with one exception. The measurements for pharmacokinetics were made after the first dose in 11 of 15 centres. One centre used a test dose 1-2 weeks prior to conditioning.

The timing of the samples for pharmacokinetic measurements in relation to the drug administration as well as the busulfan exposure target ranges varied markedly, no two centres had an identical policy. The practice of dose adjustment based on pharmacokinetics was reported to be the same in myeloablative and reduced intensity conditioning, with one exception.

Seventy-four centres adjusted the dose of busulfan in myeloablative conditioning in obese patients, whereas 25 centres did not. In RIC, 53 centres adjusted the dose whereas 31 did not. In obese patients, the busulfan dose was determined according to actual body weight (12 centres), ideal body weight (15 centres), AIBW-25 (ideal body weight + 0.25 x (actual body weight – ideal body weight) (46 centres), AIBW-40 (12 centres), or other (11 centres). The most common policy of using AIBW-25 is in line with the recommendations of the American Society of Blood and Marrow Transplantation Practice Guidelines Committee [3].

Conclusions

There is a marked variation between centres in the details of busulfan administration for conditioning in allogeneic transplantation. The clinical impact of this variation remains uncertain. Efforts toward a more standardized use of busulfan in the conditioning would be indicated.

Conflict of interest

No conflicts of interest are reported.

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Как применять бусульфан для кондиционирования при аллогенной трансплантации

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Резюме

Кондиционирующая терапия, основанная на применении бусульфана, используется в течение десятилетий при аллогенной трансплантации гемопоэтических клеток (алло-ТГСК). Ранее препарат назначали перорально. Однако индивидуальные различия в абсорбции препарата из кишечника иногда приводят к побочным токсическим эффектам. В последнее время внутривенное введение бусульфана применяют вместо перорального назначения, но многие клиники еще используют и пероральную терапию. Кроме того, различные центры применяют разные схемы его назначения, фармакокинетические исследования для индивидуализации доз препарата. Поэтому целью нашего исследования была оценка классического применения бусульфана в различных трансплантационных клиниках. Рабочая группа Европейского общества трансплантации костного мозга (EBMT) провела исследование среди сентров ТГСК относительно их практики использовании бусульфана для кондиционирования у взрослых пациентов, в том числе – дозы и пути введения препарата, роль фармакогенетического мониторинга. В большинстве клиник бусульфан назначают внутривенно, как в миелоаблативном режиме, так и в режимах сниженной интенсивности. Отмечаются значительные различия между центрами в отдельных моментах назначения бусульфана для кондиционирования. Клинические последствия такой вариабельности остаются невыясненными. Требуются усилия, направленные на более стандартизованное применение бусульфана в кондиционирующей терапии.

Ключевые слова

Бусульфан, трансплантация гемопоэтических стволовых клеток, способ назначения, дозировка, мониторинг.