Understanding treatment benefits and harms

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There is a proposal to offer coverage for a breast cancer screening program to women aged 20–40 in your Health Maintenance Organization (HMO). There are doubts about the effectiveness of such a screening program. We present here four statements derived from four randomized controlled trials published in the literature pertaining to breast cancer screening. On the basis of each statement, you should indicate how likely you are to agree to the implementation of a breast cancer screening program. Assume that the costs of each program are the same. Each result was deemed to be statistically significant.

During a 7-year follow-up:
- Program A reduced the death rate from breast cancer by 33%
- Program B produced an absolute reduction in deaths from breast cancer of 0.06%
- Program C increased the rate of survival from breast cancer from 99.82 to 99.88%
- Program D prevented one death from breast cancer for every 1666 women screened

Which program do you recommend?

If you choose program A, you are thinking like the majority of physicians,† who on first reflection identified highest number with the greatest benefit. After giving some thought to a problem (see below), we of course all understand that each program above offers identical benefits. We simply failed to appreciate the difference between relative and absolute measures in expressing treatment benefits. We are often asked (and mandated by numerous agencies and regulatory bodies) to discuss the benefits and harms of treatment interventions with our patients. But, what exactly do we mean by ‘treatment benefits and harms’? In this tutorial we will try to shed some light on this issue.

MEASURES OF BENEFITS AND HARMs ARE COMPARATIVE MEASURES BETWEEN ALTERNATIVE TREATMENT OPTIONS

It is important to remember that the question of treatment benefit is the question of comparison. When we talk about benefit of treatment A, our first question should be ‘in comparison to what?’ i.e. to treatments B, C, etc or to no treatment at all? The next question to ask is if treatment reduces bad events or increases the chances for a good event? Finally, in oncology, our patients often ask us: ‘Doc, how long do I have to live?’ asking us to estimate their life expectancy (LE).

THREE WAYS OF COMPARISON: DIFFERENCE, RELATIVE RISK (PROPORTIONS) AND RATIOS

Since the ‘bread and butter’ for data on treatment benefit comes from the analysis of survival data, we will attempt to derive clinical useful measures of treatment benefit from survival curves. Figure 1 shows data that can be derived from survival curves.‡ Let us assume that two curves represent survival data after treatment of a given cancer with standard (control) (C) therapy and new chemotherapy (experimental therapy) (E). We can compare survival probabilities for these two treatments at a point of interest (say, 5 years) in terms of: (1) direct or absolute difference as |E - C|, (2) proportionate reduction/increment as [E - C]/C, or (3) direct ratio (E/C) or (C/E).

Let us see now how these simple relationships can be converted into palpable benefits for our patients. We said above that the second step is to determine if we are increasing good events or preventing bad events. Let us say we would like to deduce from Fig. 1 the efficacy of experimental treatment in terms of survival (good event) at 5 years. We see that at 5 years, approximately 33% of patients on treatment E are estimated to be alive vs. 25% those on treatment C. This can be converted into: (1) absolute benefit increase (ABI) of 8% ([33 - 25 = 8]), (2) relative benefit increase (RBI) of 32% ([33 - 25]/25 = 32%), or (3) relative benefit of 1.32 (33/25). Note that benefit in terms of direct ratio can also be expressed as commonly used, but not that popular odds ratio (OR), which can be defined as [E/(1 - E)]/[C/(1 - C)] = 2.62, meaning that odds of survival for experimental treatment is 2.62 times higher than the odds of survival for control treatment.

Often in the literature, benefits are presented in terms of preventing bad events. In our case, the bad event is mortality, which is equal to 100-survival (%). Repeating the exercise presented above for our example, we can define the following measures of benefit: (1) absolute risk reduction (ARR) is 8%: [100 - 25 - 100 - 33] = 8, (2) relative risk reduction (RRR) is 10.7%: [(100 - 25) - (100 - 33)/100 - 25 = 10.7%], (3) relative risk is 0.76 (25/33) and OR as [C/(1 - C)]/[E/(1 - E)] = 1.5, meaning that odds of mortality for experimental treatment is 1.5 times lower than the odds of mortality for control treatment.

We should note here that in this tutorial we are not addressing hazard ratio, which is one of the most appropriate summary statistics when it comes to comparison of time-to-event data. A reader is referred to the article on survival analysis written by one of us in the last issue of EBO.†

NNT AND NNH

One very popular measure to express benefits in clinical terms is to calculate NNT, which denotes the number of patients who need to be treated with experimental therapy in order to have one additional favorable outcome in comparison with the control treatment.‡ It is equal to NNT = 1/ARR or NNT = 1/RRR, which in our case is 12.5 (and by convention this was rounded to the highest integer number, 13). This means we need to treat 13 patients with experimental treatment for 5 years to prevent one death (or save one life).

It should be obvious by now that all of these measures are equivalent. However, relative measures tend to be more impressive and are, therefore, more often used. Unfortunately, our decisions can be easily influenced by the format of presentation of the measures of benefits (and harms) as shown in the introductory example.†

It is important to note that NNT dramatically changes with the absolute difference, while RRR does not. For example, if in the
above example survival difference was 3.3 vs. 2.5%, RBI still remains 32%, but NNT dramatically increases to 125. In calculations like these it is also assumed that RRR or RBI are constant over time, which may or may not be true.

Measures of harm relate to increase in the number of bad events and can be analogously derived. They are commonly expressed as relative risk increase (RRR), absolute risk increase (ARI) and the number of patients (NNH) who, if they receive experimental treatment, would lead to one additional person being harmed compared with patients who receive the control treatment; (NNH = 1/ARR).4

DETERMINING LIFE EXPECTANCY While all measures of benefits and harms defined above are useful, they are not easily grasped by patients. Patients often want to know how many years they have to live, i.e. they want us to determine their life expectancy. This information is also available from survival curves. Life expectancy is equal to the area under survival curve (AUC) of a given treatment.5 The gain in LE(ALE) between two treatments is, thus, equal to the difference between AUC for experimental and control treatment6 (Fig. 1). However, determination of AUC is not that easy to do. Fortunately, there exists a simple method that can help us determine LE relatively accurately for most situations in oncology. This method termed declining exponential approximation of life expectancy (DEALE) is accurate when the disease-specific mortality rate exceeds 10% per year.5,10 In these cases, the error in calculation of LE is less than 1 year regardless of the age of the patient. DEALE is based on the assumption that in some diseases, such as cancer, the mortality rate (m) is constant and survival thus can be described by a declining exponential function.

According to the DEALE method the patient-specific LE is equal to

\[ LE = \frac{1}{m_p} \]

where \( m_p \) refers to patient-specific mortality. In turn, \( m_p \) is equal to sum of age-sex-race-related mortality (\( m_{ar} \)) and disease-specific mortality (\( m_d \)):

\[ m_p = m_{ar} + m_d \]

where \( m_d \) represent the mortality rates for the specific disease that the patient has. We assume here, for simplicity, that a patient has one disease. In the case that our patient has more than one disease, we would simply add together the disease-specific mortalities of all diseases. According to the DEALE an average annual mortality rate, \( m_{ar} \), is

\[ m_{ar} = -\frac{1}{t} \times \ln(S) \]

where In is the natural logarithm, \( t \) the time at which the fractional survival is measured and \( S \) the proportion of patients still alive at time \( t \). Note that \( m_{ar} \) is what is available from survival analysis in the literature.

If our patient is similar to a study population for which we have a survival curve, then \( m_{ar} = m_{ar} \). In our example (Fig. 1), the 5-year survival was 0.33 and 0.25 for experimental and control treatment, respectively. This is equal to \( m_{ar} \) of 0.22 per year for experimental and 0.277 per year for control treatment, which converts into LE of 4.5 and 3.6 years, respectively. Gain in LE with experimental treatment is, thus, equal to \( \Delta LE = 4.5 - 3.6 = 0.9 \) years.*

We should also note that the DEALE method is relevant only for those patients with a disease for which there is no cure. If the survival curve has a plateau, the area under the curve is infinite. In the case of cure, using an estimate of the probability of cure would be more appropriate than calculation of life expectancy.

It is important to understand that the gain in LE is an average value. This means that a gain in LE means that either all of the patients treated with a given therapy obtain a small increase in life span, or some patients enjoy a large increase in LE.7 Thus, the gain in LE should be interpreted probabilistically and is related to a shift in survival curve to the right (see Fig. 1). This shift implies an immediate increase in the probability of survival in comparison with control group.8 This is important to understand because it is commonly misconceived that a gain in LE means ‘adding time (years) to life’. In our example above, it means that 0.9 years (329 days) of gain in LE with experimental treatment over control is not simply added to control LE, but is rather evenly distributed resulting in an average gain of 11 months of LE (the actual increase for a given patient may be large, close to zero, or even negative).9

Second, equally effective treatments in terms of absolute or relative measures of benefit will convert into different gains in LE depending on the slope of the survival curve (i.e. baseline risk of death). If the slope of the survival curve is steeper a gain in LE will be smaller, and vice versa.10 Finally, Figure 1 shows another important piece of information often used in oncology. It refers to median survival times or the time at which half of the cohort patients have died. Note that \( m_{ar} \) can also be calculated from the median survival time as 0.693/\( t \) and used with the DEALE method.9,10

We hope that we have shown how the richness and complexity of survival curves can be translated into useful measures that help us summarize the magnitude of treatment effects. Several seemingly different measures are obtained from the same comparative data. In future tutorials we hope to show how data on benefits and harms can be used in decision-making at the bedside in individual patients.

Literature cited

*Note that if our patient’s age is different from age of patients in a study population (i.e. \( m_{ar} \neq m_{ar} \)), then \( m_{ar} \) needs to be subtracted from \( m_{ar} \) to obtain \( m_{ar} \). In the next step, patient-specific \( m_{ar} \), which can be found in the tables of vital statistics, need to be added to \( m_{ar} \) to obtain patient specific \( m_{ar} \). A reader is referred to references for details.5,10